

PRODUCT MONOGRAPH

Pr ANGELIQ[®]

Drospirenone and Estradiol-17 β tablet

1/1 mg

Progestin – Estrogen

Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario
L4W 5R6
<http://www.bayer.ca>

Date of Revision:
February 17, 2016

Submission Control No: 189314

© 2016, Bayer Inc.
® TM see www.bayer.ca/tm-mc

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS.....	12
DRUG INTERACTIONS	16
DOSAGE AND ADMINISTRATION	21
OVERDOSAGE	21
ACTION AND CLINICAL PHARMACOLOGY	22
STORAGE AND STABILITY	27
DOSAGE FORMS, COMPOSITION AND PACKAGING	27
 PART II: SCIENTIFIC INFORMATION	 28
PHARMACEUTICAL INFORMATION	28
CLINICAL TRIALS	30
DETAILED PHARMACOLOGY	33
TOXICOLOGY	35
REFERENCES	39
 PART III: CONSUMER INFORMATION.....	 42

ANGELIQ®

Drospirenone and Estradiol-17 β tablet

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Film-coated tablet, 1 mg drospirenone/1 mg estradiol-17 β	None <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

ANGELIQ (drospirenone and estradiol-17 β) is indicated for:

- treatment of the climacteric syndrome (vasomotor symptoms) in postmenopausal women. This may include the treatment of the symptoms of vulvar and vaginal dryness associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal dryness, topical vaginal products should be considered. ANGELIQ is recommended for use only in patients with an intact uterus since the regimen includes a progestin whose role is to assist in the prevention of endometrial hyperplasia.

CONTRAINDICATIONS

- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known, suspected, or personal history of estrogen-dependent or progestin-dependent malignant neoplasia (eg, breast cancer or endometrial cancer)
- Presence or history of liver tumors (benign or malignant)
- Presence or history of severe renal disease as long as renal function values have not returned to normal
- Severe hypertriglyceridemia
- Endometrial hyperplasia
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Lactation
- Active or past history of arterial thromboembolic disease (eg, stroke, myocardial infarction, coronary heart disease)
- Classical migraine

- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis
- A high risk of venous or arterial thrombosis, including known thrombophilic disorders (see **WARNINGS AND PRECAUTIONS**)
- Partial or complete loss of vision due to ophthalmic vascular disease
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n = 16 608) and oral *estrogen-alone* therapy (n = 10 739) in postmenopausal women aged 50 to 79 years. (1-3)

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increase risk of *myocardial infarction* (MI), *stroke*, *invasive breast cancer*, *pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo. (3)

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo. (1)

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

Carcinogenesis and Mutagenesis

Breast Cancer

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10 000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined Hormone Replacement Therapy [HRT] versus 30 on placebo). (3)

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean (SD) 1.7 cm (1.1) vs 1.5 cm (0.9), respectively; $P = 0.04$) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter. (2)

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo. (1)

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease. There is a need for caution in prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of HRT should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Ovarian Cancer

Some recent epidemiologic studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Liver Tumors

In rare cases, benign and even more rarely, malignant liver tumors have been observed after the use of hormonal substances such as those contained in HRT products. In isolated cases, these tumors led to life-threatening intra-abdominal hemorrhage. A hepatic tumor should be considered in the differential diagnosis if upper abdominal pain, enlarged liver, or signs of intra-abdominal hemorrhage occur.

Endometrial Hyperplasia and Endometrial Carcinoma

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer.

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. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see **CLINICAL TRIALS**).

Pituitary Tumors

Close medical supervision (including periodic measurement of prolactin levels) is necessary if the patient suffers from hyperprolactinemia, prolactinoma or is at risk of developing prolactinoma.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women. (1, 4, 5) The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women. (1, 3)

WHI Trial Findings

In the combined *estrogen plus progestin* arm of the WHI trial, among 10 000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo). (3)

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10 000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on estrogen-alone therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD. (1)

HERS and HERS II Findings

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n = 2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus 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 hormone-treated group than in the placebo group in year 1, but not during the subsequent years. (5)

From the original HERS trial, 2 321 women consented to participate in an open label extension of HERS, known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD. (4)

Blood Pressure

Women using HRT sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Ear/Nose/Throat

Estrogens should be used with caution in patients with otosclerosis

Endocrine and Metabolism

Glucose and Lipid Metabolism

A worsening of glucose tolerance and lipid metabolism has been observed in a significant percentage of peri- and postmenopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with moderately elevated levels of triglycerides need special surveillance. HRT in these women may be associated with a further increase in triglyceride levels bearing the risk of acute pancreatitis.

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Heme Metabolism

Women with porphyria need special surveillance.

Calcium and Phosphorus Metabolism

Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Hypothyroidism

Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see [Drug-Laboratory Test Interactions](#)).

Genitourinary

Vaginal Bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt diagnostic measures like hysteroscopy, endometrial biopsy, or curettage to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Uterine Leiomyomata

Pre-existing uterine leiomyoma may increase in size during estrogen use. Growth, pain, or tenderness of uterine leiomyoma requires discontinuation of medication and appropriate investigation.

Endometriosis

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use. Should endometriosis be reactivated under treatment, discontinuation of therapy is recommended.

Hematologic

Venous Thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10 000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism. (3)

In the *estrogen-alone* arm of the WHI trial, among 10 000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism. (1)

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index $>30 \text{ kg/m}^2$), and systemic lupus erythematosus. The risk of VTE also increases with age and smoking. The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. HRT should not be prescribed in case of a negative risk benefit assessment.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Benefit/risk should therefore be carefully weighed in consultation with the patient when prescribing HRT to women with a risk factor for VTE.

Hepatic/Biliary/Pancreatic

Gallbladder Diseases

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

Hepatic hemangioma

Particular caution is indicated in women with hepatic hemangiomas as estrogens may cause an exacerbation of this condition.

Jaundice

Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver Function Tests

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under **Monitoring and Laboratory Tests**.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema. Discontinuation of this medication should be considered.

Systemic lupus erythematosus

Particular caution is indicated in women with systemic lupus erythematosus.

Neurologic

Cerebrovascular Insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be re-evaluated.

Dementia

Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women aged 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (*estrogen plus progestin* or *estrogen-alone*) reduces the risk of dementia in women aged 65 and over and free of dementia at baseline. (6, 7)

In the *estrogen plus progestin* arm of the WHIMS (n = 4 532), women with an intact uterus were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10 000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo). (7)

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10 000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on estrogen-alone versus 25 on placebo), although this difference did not reach statistical significance. (6)

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10 000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on estrogen plus progestin or estrogen-alone versus 23 on placebo). (6)

Epilepsy

Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

Renal

Fluid Retention

Estrogens with or without progestins may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Nonsevere disturbances of liver function, including hyperbilirubinemias such as Dubin-Johnson syndrome or Rotor syndrome, require close supervision. In case of deterioration of markers of liver function, the use of HRT should be discontinued.

Skin

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 HRT.

Other Conditions

The following conditions have been reported to occur or deteriorate with HRT use. Although the evidence of an association with HRT use is inconclusive, women with these conditions and treated with HRT should be carefully monitored:

Asthma; benign breast disease; chorea minor; epilepsy; otosclerosis; porphyria; systemic lupus erythematosus.

Special Populations

Pregnant Women

ANGELIQ must not be used during pregnancy and lactation (see **CONTRAINDICATIONS**). If pregnancy occurs during medication with ANGELIQ, treatment must be discontinued immediately.

Monitoring and Laboratory Tests

Before ANGELIQ (drospirenone and estradiol-17 β) is administered, the patient should have a complete physical examination, including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurement of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3 to 6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician. It is important that patients are encouraged to practice frequent self-examination of the breasts.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See **WARNINGS AND PRECAUTIONS** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combinations in general:

Blood and Lymphatic System Disorders: Altered coagulation tests (see **DRUG INTERACTIONS, Drug-Laboratory Test Interactions**).

Cardiac Disorders: Palpitations; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**); coronary thrombosis

Ear and Labyrinth Disorders: otosclerosis¹

Endocrine Disorders: Increased blood sugar levels; decreased glucose tolerance or changes in effect on peripheral insulin resistance; prolactinoma

Eye Disorders: Neuro-ocular lesions (eg, retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses

Gastrointestinal Disorders: Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating)

General Disorders and Administration Site Conditions: Fatigue; changes in appetite; changes in body weight; change in libido

Hepatobiliary Disorders: Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice; benign and malignant hepatic tumors

Immune System Disorders: asthma¹; hypersensitivity (including symptoms such as rash and urticaria); systemic lupus erythematosus¹

Metabolism and Nutrition Disorders: hypertriglyceridemia; porphyria¹

Musculoskeletal and Connective Tissue Disorders: Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3 to 6 weeks) may occur

Nervous System Disorders: Aggravation of migraine episodes; headaches, dizziness; neuritis; chorea minor¹; epilepsy¹

Psychiatric Disorders: Mental depression; nervousness; irritability; dementia

Renal and Urinary Disorders: Cystitis; dysuria; sodium retention; edema

Reproductive System and Breast Disorders: Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; premenstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness; benign breast disease¹; increase in size of uterine fibroids

Skin and Subcutaneous Tissue Disorders: Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism and acne

Vascular Disorders: Isolated cases of: thrombophlebitis; thromboembolic disorders

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema (see **WARNINGS AND PRECAUTIONS**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information

¹ Occurrence or deterioration of conditions for which association with HRT use is not conclusive

from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A clinical trial dataset of 1 532 patients was used to generate the adverse drug reaction profile of ANGELIQ to support market authorization in Canada (market authorization clinical trials dataset). Subsequent to market introduction, additional adverse drug reaction data from clinical trials (n = 892) has become available for a total database of 2 424 patients.

Market Authorization Clinical Trials Dataset

The most commonly reported adverse reaction to ANGELIQ (drospirenone and estradiol-17 β) in the clinical trials upon which market authorization is based (n = 1 532) were breast pain, vaginal bleeding, abdominal pain, headache, enlarged abdomen, breast neoplasm, asthenia, depression, hot flashes, emotional lability, nausea, enlarged uterine fibroids, cervix neoplasm, leukorrhea, fibrocystic breast, pain in extremity, nervousness, breast enlargement, peripheral edema, and vaginitis.

The following are adverse events reported with ANGELIQ treatment in these clinical trials, including strengths of drospirenone in combination with estradiol that are not approved (ie, containing 1, 2, or 3 mg DRSP):

Table 2: Adverse Events Considered at Least Possibly Related to ANGELIQ in Four Phase III Clinical Trials (n = 1 532)

Organ System	Adverse Event	
	Common ($\geq 1/100$, $< 1/10$)	Uncommon ($\geq 1/1\ 000$, $< 1/100$)
Body as a Whole	Abdominal pain Asthenia Pain in extremity	Pain in back or pelvis Chills Malaise Laboratory test abnormal
Cardiovascular System		Migraine Hypertension Chest pain Palpitation Varicose veins Venous thrombosis Superficial thrombophlebitis Vasodilation
Digestive	Nausea	Gastrointestinal disorder Increased appetite Liver function test abnormal
Metabolic and Nutritional Disorders		Generalized or localized edema Weight gain Hyperlipemia
Musculoskeletal System		Muscle cramps Arthralgia
Nervous System	Headache Mood swings Hot flushes Nervousness	Insomnia Dizziness Libido decreased Concentration ability impaired Paresthesia Sweating increased Anxiety Dry mouth Vertigo
Respiratory System		Dyspnea
Skin and Appendages	Benign breast neoplasms Breast enlargement	Alopecia Skin or hair disorder Hirsutism Breast carcinoma Breast engorgement
Special Senses		Taste disturbance
Urogenital	Uterine fibroids enlarged Cervix neoplasm Leukorrhea	Vulvovaginitis Endometrial or cervical disorder Bleeding Dysmenorrhea Ovarian cyst Urinary tract infections
		Incontinence

Additional Related Adverse Drug Reactions

The following *additional* adverse drug reactions were observed in clinical trials (n = 2 424), including strengths of drospirenone in combination with estradiol that are not approved in Canada (ie, containing 0.5, 1, 2, or 3 mg DRSP), and are considered at least possibly related to ANGELIQ by the investigator:

Uncommon ($\geq 1/1\ 000$, $< 1/100$)

Cardiovascular System: Embolism

Digestive System: Anorexia, constipation, diarrhea, flatulence, vomiting

Metabolic and Nutritional Disorders: Weight loss

Skin and Appendages: Acne, pruritus, rash

Special Senses: Abnormal vision, eye disorder

Rare ($< 1/1\ 000$)

Digestive System: Cholelithiasis

Hematic and Lymphatic: Anemia

Skin and Appendages: Tinnitus

Urogenital System: Salpingitis

The following adverse reactions, considered at least possibly related to ANGELIQ were recorded in 2 clinical trials in hypertensive women: hyperkalemia, cardiac failure, atrial flutter, QT interval prolonged, cardiomegaly, blood aldosterone increased.

Postmarket Adverse Drug Reactions

The following adverse reactions have been identified from postmarketing experience with the use of ANGELIQ: venous and arterial thromboembolic events (peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction and stroke not specified as hemorrhagic) (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Hematologic**), breast cancer (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Carcinogenesis and Mutagenesis**).

If adverse symptoms persist, the prescription of HRT should be re-considered.

DRUG INTERACTIONS

Overview

Estrogens may diminish the effectiveness of anticoagulants, antidiabetics, and antihypertensive agents.

Preparations inducing liver enzymes (eg, barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, or rifampicin) may interfere with the activity of orally administered estrogens.

Drug-Drug Interactions

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampicin) on plasma concentrations of synthetic steroids.

Effects of Drospirenone on Other Drugs

Metabolic Interactions

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in in vitro and in vivo studies (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**). In in vitro studies, DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women (including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype), the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose). Based on the available results of in vivo and in vitro studies, it can be concluded that, at clinical dose level, DRSP is unlikely to interact significantly with cytochrome P450 enzymes.

Effects of Other Drugs on Clearance of HRTs

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme induction)

Estrogens are metabolized partially by cytochrome P450 enzymes (e.g. CYP3A4). Interactions can occur with drugs that induce CYP enzymes which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

CYP enzyme inducers include phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

Substances with variable effects on the clearance of sex hormones

When co-administered with sex hormones, many anti-HIV protease inhibitors (eg, nelfinavir, ritonavir, ritonavir-boosted protease inhibitors), HCV protease inhibitors (eg, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (eg, nevirapine) can increase or decrease plasma concentrations of estrogen or progestin or both. These changes may alter the safety and effectiveness of ANGELIQ. Healthcare providers should refer to the label of the

individual anti-HIV/HCV protease inhibitor or non-nucleoside reverse transcriptase inhibitor for further drug-drug interaction information.

Substances decreasing the clearance of sex hormones (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (eg, fluconazole, itraconazole, ketoconazole, voriconazole,), verapamil, macrolides (eg, clarithromycin, erythromycin), diltiazem and grapefruit juice, can increase plasma concentrations of the estrogen or the progestin or both. The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Coadministration with Drugs that Have the Potential to Increase Serum Potassium

Nonsteroidal Anti-inflammatory Drugs (NSAID)

The interaction of DRSP 3 mg/E2 1 mg and indomethacin was studied in 32 postmenopausal women who were coadministered 150 mg indomethacin daily for 17 days. No subject developed hyperkalemia during the study. A complete 24 hour serum potassium profile showed no clinically or statistically significant difference between serum potassium concentrations in subjects on indomethacin alone or the combination of DRSP/E2 + indomethacin. The combined intake of a potent NSAID, indomethacin and DRSP 3 mg/E2 1 mg did not cause hyperkalemia in healthy postmenopausal women.

ACE Inhibitors or Angiotensin Receptor Blockers (ARB) + Nonsteroidal Anti-inflammatory Drugs (NSAID)

Combined effects of an ACEI or ARB with an NSAID were studied in 230 postmenopausal women with hypertension and/or diabetes mellitus requiring an ACE inhibitor or angiotensin receptor blocker (ARB). Of these, 26 patients had a creatinine clearance >50 mL/min to <80 mL/min. Patients were given DRSP 3 mg/E2 1 mg or placebo over 28 days. Nondiabetic patients also received ibuprofen 1200 mg/day for 5 days during the study. The range of mean serum potassium values during the treatment phase was similar in both groups, 4.35 to 4.42 mEq/L for the DRSP/E2 group and 4.27 to 4.34 mEq/L for the placebo group. After 28 days of exposure the mean change from baseline for the DRSP/E2 group was 0.11 mEq/L and 0.08 mEq/L for the placebo group.

Serum potassium levels ≥ 5.5 mEq/L were observed in 8 (7.3%) DRSP/E2-treated subjects (3 diabetic and 5 nondiabetic) and 3 (2.6%) placebo-treated subjects (2 diabetic and 1 nondiabetic). None of the subjects with serum potassium levels ≥ 5.5 mEq/L had cardiovascular adverse events. The elevated levels returned to normal even with continuous treatment. The addition of ibuprofen resulted in a slight increase in the number of subjects with potassium values greater than 5.5 mEq/mL. The addition of an NSAID can increase the risk of elevated potassium in both diabetics and nondiabetics receiving ACEI and ARBs. DRSP/E2 administered concomitantly slightly increases the probability of elevated potassium, although the results were not statistically significant.

ACE Inhibitors

A 2-week study in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily with placebo or DRSP 3 mg/E2 1 mg was performed to assess the effect on serum potassium. Of them, 8 had mild renal insufficiency. Potassium levels were obtained every other day. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. The ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group experienced serum potassium above the upper limit of normal.

Physicians and other health care providers should be aware of other nonprescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

Coadministration with Drugs that Have the Potential to Decrease Serum Potassium

Hydrochlorothiazide

A 4-week study in 36 mildly hypertensive postmenopausal women taking hydrochlorothiazide (HCTZ) 25 mg once daily with placebo or DRSP 3 mg/E2 1 mg was performed to assess potential interactions with HCTZ. The pharmacokinetics of HCTZ was not affected by coadministration with DRSP 3 mg/E2 1 mg. Therefore, no dosage adjustment is required when administering ANGELIQ with HCTZ.

Drug-Food Interactions

The effect of food on the absorption and bioavailability of DRSP and E2 have not been investigated following the administration of ANGELIQ. However, clinical studies with formulations containing DRSP or E2 have shown that the bioavailability of both drugs is not affected by concomitant food intake.

Drug-Herb Interactions

It was found that some herbal products (eg, St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be made aware of the other nonprescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T₄) as measured by column or radioimmunoassay; free T₃ resin uptake is decreased, reflecting the elevated TBG; free T₄ concentration is unaltered
- other binding proteins may be elevated in serum, ie, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively; free or biologically active hormone concentrations are unchanged (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).
- impaired glucose tolerance
- reduced serum folate concentration
- increased serum triglyceride and phospholipid concentration

In Study 96097 on endometrial safety, additional metabolic variables were investigated as safety variables in a subgroup of 210 patients. No relevant changes in insulin and glucose levels in the oral glucose tolerance tests performed after one year of treatment with the E2/DRSP combinations were observed. Overall, none of the E2/DRSP combinations impaired glucose tolerance. In addition, a number of coagulation parameters including activated partial thromboplastin time, fibrinogen level, and plasminogen activator inhibitor level were tested. These coagulation parameters generally decreased during treatment with E2 alone, as well as with the combinations of 1 mg E2 with 0.5 to 3 mg DRSP. The decreases of the activated partial thromboplastin time were statistically significant for all E2/DRSP combinations, the decrease in plasminogen activator inhibitor levels was only significant for the combination of 1 mg E2 with 3 mg DRSP, and the decrease in the fibrinogen levels was significant only for E2 alone. This hormone-associated reduction of plasminogen activator inhibitor was observed despite increased levels of triglycerides, which are known to induce the levels of plasminogen activator inhibitor.

The magnitude of the observed changes was small. It should also be noted that a predictive value of these changes for the risk of VTEs is not established.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks. The pathologist should be informed that the patient is receiving estrogen/progestin therapy when relevant specimens are submitted.

Drug-Lifestyle Interactions

Interaction with alcohol

Acute alcohol ingestion during use of HRT may lead to elevations of circulating estradiol levels.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ANGELIQ tablets are a combination of estradiol-17 β (estrogen) and drospirenone (progestin) intended for continuous administration as hormone replacement therapy (HRT). Women who do not take estrogens or women who change from a continuous combination product may start treatment at any time. Patients changing from a sequential combined HRT regimen should be started at the end of the scheduled bleeding.

Recommended Dose and Dosage Adjustment

One tablet is taken daily. Each blister pack is for 28 days of treatment. The tablets are to be swallowed whole with some liquid, irrespective of food intake. There is no need for the patient to count days between cycles because there are no "pill-free days". The tablets should be taken at the same time every day.

Missed Dose

In the case of a missed tablet, it should be taken as soon as possible. If more than 24 hours have elapsed, no extra tablet needs to be taken. If several tablets are forgotten, bleeding may occur. Irregular uterine bleeding may occur, particularly in the first 6 months, but generally decreases with time, and eventually may lead to an amenorrheic state. Patients should be re-evaluated after the first three months of therapy, then at regular (ie, three to six months) intervals or if significant bleeding occurs after three months.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms of Overdose

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin (eg, norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne, and hirsutism.

Treatment of Overdose

In the event of a possible overdose, the physician should observe the patient closely and symptomatic treatment should be given.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ANGELIQ is a continuous dosage regimen of an estrogen-progestin combination for oral administration as hormone replacement therapy (HRT). ANGELIQ contains 17 β -estradiol, which is chemically and biologically identical to endogenous human estradiol, and the synthetic progestin, drospirenone. 17 β -estradiol provides hormone replacement during and after the climacteric. The addition of drospirenone opposes the development of endometrial hyperplasia thought to be caused by estrogens.

Pharmacodynamics

Clinical Pharmacology of Estrogens

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol-17 β (E2) is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estrinol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 μ g of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulphate conjugated form, estrone sulphate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism. Estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Loss of ovarian estradiol-17 β production after menopause can result in instability of thermoregulation, causing hot flashes associated with sleep disturbance and excessive sweating. Estrogen replacement therapy is effective in reducing the number and intensity of hot flashes associated with menopause.

Clinical Pharmacology of Progestins

Drospirenone (DRSP), a spironolactone analogue, is a progestogen with antimineralocorticoid activity. Similar to spironolactone and endogenous progesterone, drospirenone affects the rennin-angiotensin-aldosterone system (RAAS) by competitive binding to the aldosterone

receptor. As an aldosterone antagonist, drospirenone may retain potassium and cause excess amounts of sodium to be excreted.

In animals, drospirenone has no glucocorticoid or antiglucocorticoid activity. Drospirenone is devoid of estrogenic and androgenic activity but is antiandrogenic in animal and in vitro models.

Drospirenone has no effect on glucose tolerance and insulin resistance. In women, glucose tolerance is not compromised by the use of ANGELIQ.

Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin, in adequate doses and appropriate duration, to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with an intact uterus.

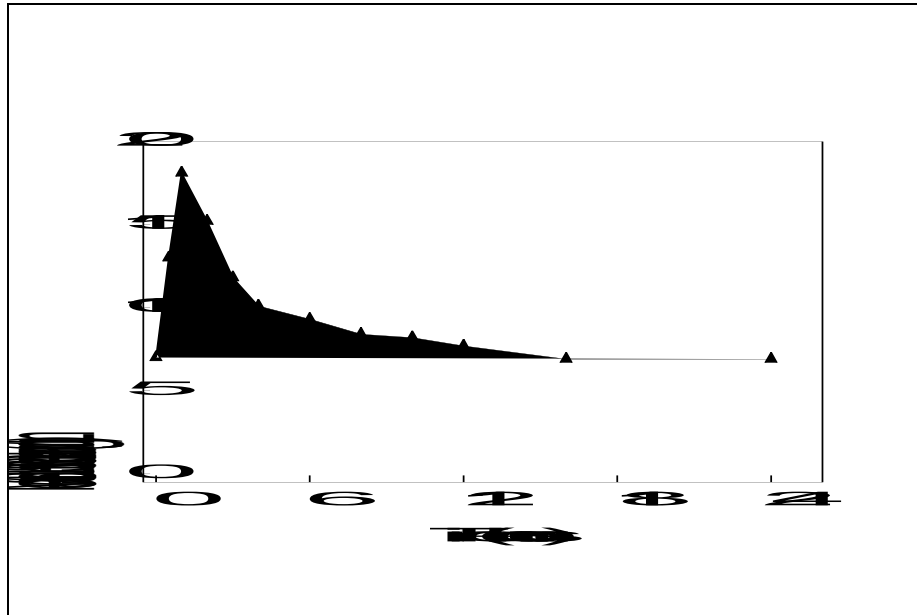
Pharmacokinetics

This section makes reference to strengths of DRSP in combination with E2 that are not approved (ie, strengths other than 1 mg DRSP/1 mg E2).

Absorption

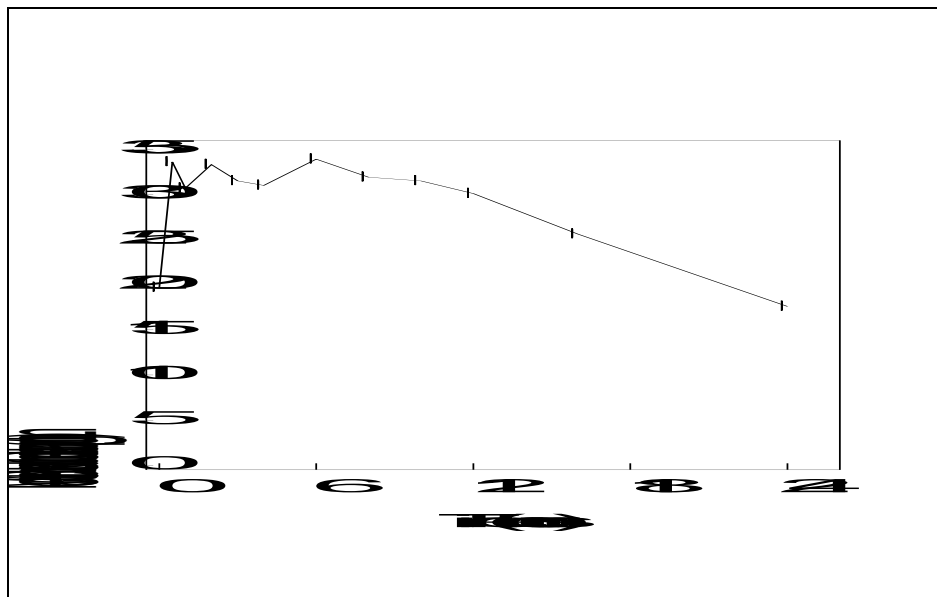
DRSP is rapidly and almost completely absorbed following oral administration. Its absolute bioavailability ranges between 76% to 85%. Serum concentrations of DRSP reached peak levels within approximately 1 hour after administration of ANGELIQ. Estradiol is well absorbed through the gastrointestinal tract. Following oral administration of ANGELIQ, peak serum estradiol concentrations are typically reached 6 to 8 hours after dosing. The oral relative bioavailability of estradiol and DRSP following administration of ANGELIQ is 107% and 102%, respectively, when compared to a combination oral microcrystalline suspension.

The pharmacokinetics of DRSP are dose proportional within the dose range of 1 to 4 mg. Following daily dosing of ANGELIQ, steady-state DRSP concentrations were observed after 10 days. Mean accumulation ratios for estradiol and DRSP were 1.9 and 2.4, respectively. Mean steady-state serum concentrations are shown in [Figure 1a](#) and [1b](#) and a summary of primary pharmacokinetic parameters following the administration of ANGELIQ for 28 days is presented in [Table 3](#).



Abbreviations: DRSP = drospirenone; mL = milliliter; ng = nanogram

Figure 1a: Mean Steady-State Serum Drospirenone Concentrations Following Repeated Daily Oral Administration of 1 mg DRSP/1mg Estradiol (n=18)



Abbreviations: mL = milliliter; pg = picogram

Figure 1b: Mean Steady-State Serum Estradiol Concentrations Following Repeated Daily Oral Administration of 1 mg DRSP/1mg Estradiol (n=18)

Table 3: Mean Steady-State Pharmacokinetic Parameters of ANGELIQ Tablets (Drospirenone and Estradiol)

Drospirenone (Mean^a ± SD)					
Dose	No. of Subjects	C_{max} (ng/mL)	t_{max} (h)	AUC_(0-24h) (ng•h/mL)	t_{1/2} (h)
1mg E2/1mg DRSP	14	18.3± 5.55	1.07±0.27	208±83	42.3±21.3
1mg E2/4mg DRSP	16	74.2±16.3	1.34±0.89	865±258	35.6±6.30
Estradiol (Mean ± SD)					
Dose	No. of Subjects	C_{max} (ng/mL)	t_{max} (h)	AUC_(0-24h) (ng•h/mL)	t_{1/2} (h)
1mg E2/ 1mg DRSP	14	43.8± 10.0	4.8±4.4	665±178	NA
1mg E2/ 4mg DRSP	16	44.6±18.4	3.8±2.6	683±330	NA
Estrone (Mean ± SD)					
Dose	No. of Subjects	C_{max} (ng/mL)	t_{max} (h)	AUC_(0-24h) (ng•h/mL)	t_{1/2} (h)
1mg E2/ 1mgDRSP	14	245± 50.6	4.2±1.3	3814±1159	23±6.2
1mg E2/ 4mgDRSP	16	283±143	4.1±1.6	4254±2121	22.4±4.5

NA = Not available, C_{max}=Maximum serum concentration, AUC=area under the curve, t_{max}=time of maximum serum concentration, t_{1/2}= half-life, SD= standard deviation.

^a arithmetic mean

Effect of Food: The effect of food on the absorption and bioavailability of DRSP and E2 have not been investigated following the administration of ANGELIQ. However, clinical studies with formulations containing DRSP or E2 have shown that the bioavailability of both drugs is not affected by concomitant food intake.

Distribution

DRSP does not bind to sex hormone-binding globulin (SHBG) or corticosteroid-binding globulin (CBG) but binds about 97% to serum protein, thought to be albumin. The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to SHBG (37%) and to albumin (61%), while only approximately 1% to 2% is unbound.

Metabolism

DRSP is extensively metabolized after oral administration. The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP, generated by opening of the lactone ring, and the 4,5-dihydrodrospirenone-3-sulfate, formed by reduction and subsequent sulfation. These metabolites were shown not to be pharmacologically active. DRSP is also subject to oxidative metabolism catalysed by CYP3A4.

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic

recirculation via sulphate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulphate conjugates, especially estrone sulphate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

DRSP serum levels are characterized by a terminal elimination half-life of approximately 36 to 42 hours. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38% to 47% of the metabolites in urine were glucuronide and sulphate conjugates. In feces, about 17% to 20% of the metabolites were excreted as glucuronides and sulphates. Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulphate conjugates.

Special Populations and Conditions

Geriatrics (> 65 years of age)

ANGELIQ should not be used in geriatric patients (> 65 years of age) as there are no studies showing benefits to geriatric patients.

Pediatrics

No pharmacokinetic study for ANGELIQ has been conducted in a pediatric population. ANGELIQ is not indicated in the pediatric population.

Gender

ANGELIQ is indicated for use in women only.

Race

No studies were done to determine the effect of race on the pharmacokinetics of ANGELIQ.

Hepatic Insufficiency

ANGELIQ is contraindicated in patients with active hepatic dysfunction or disease (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

The safety and the pharmacokinetics of a single dose of DRSP 3 mg/E2 1 mg was evaluated in 10 female patients with moderate hepatic impairment and 10 healthy female subjects matched for age, weight, and smoking history. Small changes (not statistically significant) in serum potassium were observed, although clinical significance cannot be determined. DRSP was rapidly absorbed reaching equal peak serum DRSP for both groups of subjects. However, the

total exposure of DRSP in the patients with moderate hepatic impairment was almost doubled compared to that of the normal volunteers due to prolongation of the DRSP half-life.

Renal Insufficiency

ANGELIQ is contraindicated in patients with severe renal insufficiency (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

The effects of severe renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effects of DRSP on serum potassium levels were investigated in female subjects (n = 28, age 30-65) with normal (11 patients) renal function and mild (10 patients) and moderate (7 patients) renal impairment. All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium-sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, serum DRSP levels in the group with mild renal impairment (creatinine clearance CL_{Cr}, 50-80 mL/min) were comparable to those in the group with normal renal function (CL_{Cr}, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL_{Cr}, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium-sparing drugs during the study, individual mean serum potassium levels increased by up to 0.33 mEq/L (to 4.67 mEq/L), which is well within the normal serum potassium range.

STORAGE AND STABILITY

Store in original packaging between 15°C and 30°C. Do not refrigerate or freeze. **Keep out of the reach of children and pets.**

DOSAGE FORMS, COMPOSITION AND PACKAGING

ANGELIQ tablets (drospirenone and estradiol-17β) 1 mg/1 mg are available as round, biconvex, dark pink, film-coated tablets marked on one side with the letters “DU” inside a regular hexagon. ANGELIQ is available in cartons of 1 blister pack containing 28 tablets.

Composition: Each film-coated tablet contains 1.0 mg of drospirenone and 1.0 mg of estradiol. Nonmedicinal ingredients: corn starch, ferric oxide pigment, hydroxypropylmethyl cellulose, lactose monohydrate, macrogol 6000, magnesium stearate, modified starch, povidone 25000, talc, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

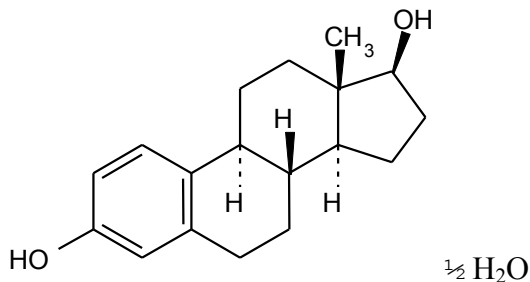
PHARMACEUTICAL INFORMATION

Drug Substance

Estradiol-17 β

Common Name:	estradiol hemihydrate, Ph.Eur.
Chemical Name:	estra-1,3,5(10)-triene-3,17 β -diol, hydrate (2:1) (CAS 9 CI)
Molecular Formula:	$C_{18}H_{24}O_2 \cdot \frac{1}{2}H_2O$
Molecular Weight:	281.40

Structural Formula:



Physical Form:	White to off-white crystals or crystalline powder
Melting Point:	173°C to 180°C
Solubilities:	Practically insoluble in water, freely soluble in alcohol, and soluble in acetone, dioxane, and other organic solvents.

Drospirenone

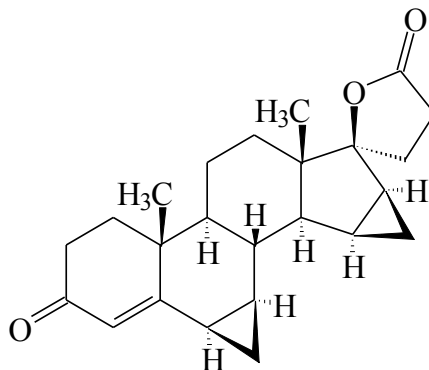
Common Name: drospirenone

Chemical Name: 6 β , 7 β ; 15 β , 16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21, 17-carbolactone (IUPAC)

Molecular Formula: C₂₄H₃₀O₃

Molecular Weight: 366.50

Structural Formula:



Physical Form: White to off-white crystalline powder

Melting Point: 199°C to 201°C

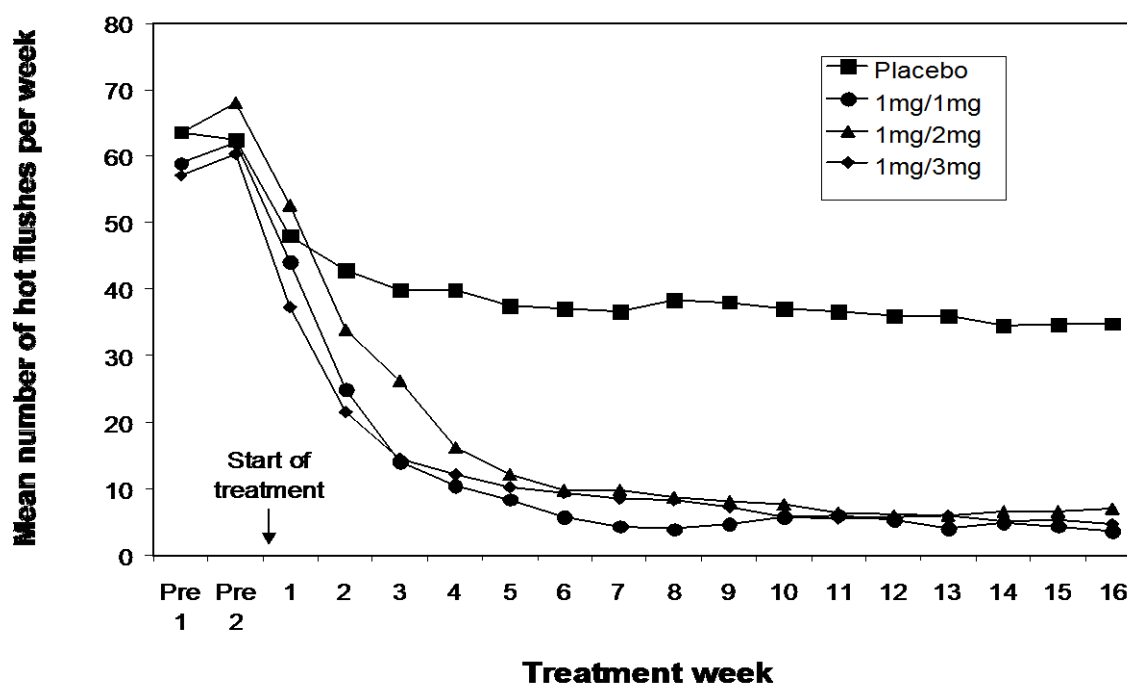
Solubilities: Freely soluble in dichloromethane; soluble in acetone, methanol, ethyl acetate, dimethoxyethane, and toluene; sparingly soluble in ethanol, and practically insoluble in water, n-hexane, and diisopropyl ether.

CLINICAL TRIALS

This section makes reference to strengths of DRSP in combination with E2 that are not approved (ie, strengths other than 1 mg DRSP/1 mg E2).

Effects on Vasomotor Symptoms

Efficacy in the treatment of climacteric symptoms was shown through demonstration of efficacy on hot flushes in postmenopausal patients who had at least five moderate to severe hot flushes per day before treatment. The respective phase II/III Study 96082, was a placebo-controlled, randomized, double-blind, multicenter study with four treatment groups (placebo, and 1 mg E2 combined with 1, 2, and 3 mg DRSP) and a treatment duration of four months. Frequency and intensity of hot flushes were monitored using the patients' daily diary entries. The mean number of hot flushes dropped from around 60 per week at baseline by 45% during treatment with placebo, and by 90%, 87%, and 86% respectively during treatment with the combinations of 1 mg E2 with 1, 2, and 3 mg DRSP. The differences between each active treatment and placebo were statistically significant. The maximum treatment effect was almost achieved after five treatment weeks (Figure 2). Since differences in the DRSP dose did not influence efficacy, it can be assumed that the effect is entirely due to E2.



Abbreviations: mg = milligram

Figure 2: Mean Number of Hot Flushes per Patient per Week (Study 96082)

In Study 97182, the severity and intensity of hot flushes was also monitored as a secondary efficacy variable. The combinations of 1 mg E2 with 2 and 3 mg DRSP were compared to the combination of 0.625 mg CEE with 5 mg MPA in an open-label study design. Participating women had to be postmenopausal, but the presence of climacteric symptoms was not an inclusion criterion. The proportion of women with hot flushes dropped from around 70% at baseline to below 30% in week 4 and to below 10% in week 12, and stayed at around 5% until the end of the two-year treatment. No relevant differences between all three treatments were observed indicating similar efficacy of 1 mg E2 and 0.625 mg CEE.

In Study 96097, the mean weekly number of moderate to severe hot flushes showed differences between treatment groups at baseline (range 14.6 to 31.8). Within each group, a statistically significant decrease in the frequency of moderate and severe hot flushes from baseline was observed at all time points beginning at week 2. The absolute number of moderate to severe hot flushes dropped to below five per week after four treatment weeks and to below three per week after eight weeks in all treatment groups. Differences between the E2/DRSP combinations and E2 alone were not statistically significant.

Overall, ANGELIQ rapidly and effectively reduced the intensity and severity of hot flushes with a maximal effect reached after only a few weeks and lasting for at least two years. Since the DRSP dose did not play a role in any of the studies it can be assumed that efficacy on hot flushes is entirely due to E2.

Effects on Other Menopausal Symptoms and Urogenital Symptoms

The E2/DRSP combinations also reduced the frequency and intensity of other menopausal symptoms and urogenital symptoms as shown by descriptive data from Studies 96082, 97182, and 96097. In the four-month symptom Study 96082, sweating episodes and sleep problems were affected the most by the E2/DRSP combinations with a reduction in the incidence of approximately 60% to 70% compared to 30% by placebo. The extent of reduction in the incidence of depression, nervousness, vaginal dryness, and nocturia was also greater in the active treatment arms than in the placebo arm. For urogenital symptoms, the data were less conclusive. The E2/DRSP combinations were more effective in the treatment of vaginal dryness and nocturia than placebo, whereas, for pollakiuria, no clear difference between placebo and the E2/DRSP combinations was detectable. A difference between the combinations with 1, 2, and 3 mg DRSP was not apparent for any symptom. In the two-year comparative Study 97182 with the combinations of 2 and 3 mg DRSP and a tablet containing 0.625 mg conjugated estrogens and 5 mg medroxyprogesterone acetate (MPA), the descriptive data suggested that all three preparations were effective in the treatment of sweating periods, sleep problems, depressed moods, and nervousness. The incidences of the urogenital symptoms (vaginal dryness, increased frequency of urination, and nocturia) were also decreased, although to a lesser extent than the central nervous symptoms. In Study 96097, urogenital symptoms were assessed during treatment with 1 mg E2 alone and with combinations of 1 mg E2 with 0.5, 1, 2, and 3 mg DRSP. The data showed a trend towards improvement of vaginal dryness, pain during intercourse, frequent urination, and night time urination in all treatment groups, except for the group receiving 1 mg E2 with 1 mg DRSP.

Effects on Endometrium

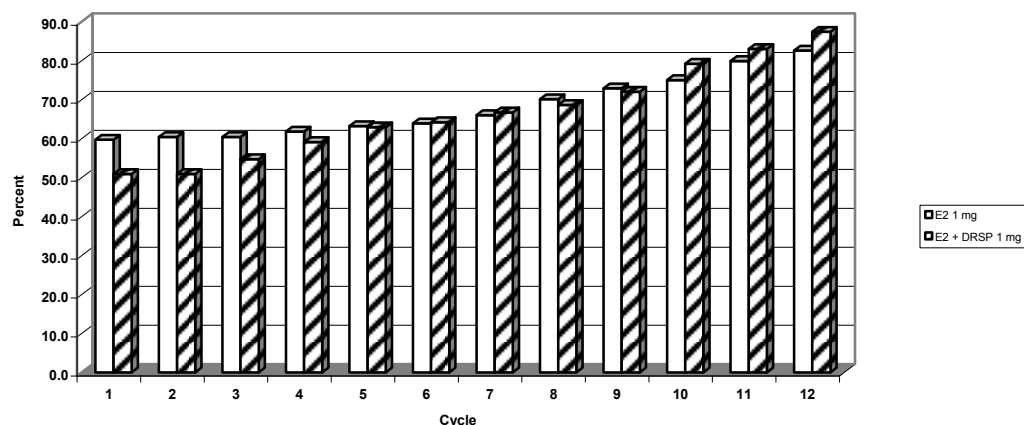
In a one-year clinical trial of 1,142 postmenopausal subjects treated with E2 alone or E2 + 0.5, 1, 2, or 3 mg DRSP, endometrial biopsies were performed on 966 (84.6%) subjects during the treatment period. Eight subjects in the E2 monotherapy group developed endometrial hyperplasia and one subject in the 1 mg E2 + 2 mg DRSP group developed simple hyperplasia with no cytological atypia. Table 4 shows that there were no diagnoses of endometrial hyperplasia in the ANGELIQ group.

Table 4: Incidence of Endometrial Hyperplasia in a 1-Year Clinical Trial

	E2 1 mg		ANGELIQ (DRSP 1 mg and E2 1 mg)	
Total No. of Subjects	226		231	
Total No. of Biopsies	197	(87.2%)	191	(82.7%)
No endometrial tissue / Tissue insufficient for diagnosis	13	(6.6%)	19	(10.0%)
Normal endometrium	141	(71.6%)	169	(88.4%)
Endometritis/ Other inflammatory/reactive states	0	(%)	0	(%)
Proliferative pattern, disordered type	35	(17.8%)	3	(1.6%)
Simple hyperplasia with no atypia	4	(2.0%)	0	(%)
Complex hyperplasia with no atypia	3	(1.5%)	0	(%)
Complex hyperplasia with cytological atypia	1	(0.5%)	0	(%)

Endometrial atrophy/inactive endometrium was achieved in 72% to 77% of women after 12 months of treatment with combination DRSP/E2. DRSP/E2 opposes the development of estrogen-induced endometrial hyperplasia effectively.

Effects on Bleeding Patterns



Abbreviations: DRSP = drospirenone; E2 = ethinyl estradiol; mg = milligram

Figure 3: Cumulative proportion of subjects at each cycle with no bleeding through the end of cycle 12

During the first few months of treatment, bleeding and spotting are quite common but decrease over time. In a cumulative analysis performed over 12 months in a double-blind trial of 1 142 postmenopausal women, the proportions of women with amenorrhea increased from 50% in the first treatment cycle to over 60% in cycle 6 and at one year 87.4% of subjects on E2 + DRSP 1 mg reported no bleeding.

Effects on Lipids

In a subgroup of subjects from the double-blind study of 1 142 postmenopausal women, lipid profile testing for subjects from selected study centers was performed at a special lipid laboratory. The results are shown in [Table 5](#).

Table 5: Mean Change in Lipid Profile from Baseline (Absolute Change - Endpoint)

Parameter (mg/dL)	E2 1 mg N=22 ^a	E2 1 mg & DRSP 1 mg N=25
Total Cholesterol	-1.4	-17.2
Triglycerides	6.1	-5.9
HDL Cholesterol	8.0	3.0
LDL Cholesterol	-7.8	-15.6

Abbreviations: DRSP = drospirenone; E2 = estradiol; HDL = high density lipoprotein; LDL = low density lipoprotein

- a One subject was excluded from the calculation since not all of her 4 parameters were available at screening visit and at endpoint.

Effects on Serum Potassium

In a double-blind controlled study of 1 142 postmenopausal women evaluated for endometrial safety with E2 1 mg or the combination DRSP/E2, there was no statistically significant difference between groups and no dose-related increases in the incidence of hyperkalemia (serum potassium > 5.5mEq/L) in subjects receiving doses up to 3 mg of DRSP. These observations do not appear to have any clinical significance. In this study, 876 subjects completed an average of 304 days on therapy. In a subset of 569 patients who were concomitantly using NSAIDs or ACEIs, only 9 had a serum potassium of >5.5mEq/L without any associated adverse event.

In a review of 1 253 patients treated with DRSP, 220 had a creatinine clearance >50 mL/min but <80 mL/min, and 12 patients had a creatinine clearance >30 but <50 mL/min. Within this cohort, no serum potassium exceeded 5.5 mEq/L.

DETAILED PHARMACOLOGY

Animal Pharmacology

Drospirenone exhibits potent progestational activity in a variety of animal models. In ovariectomized pregnant rats treated with drospirenone 3 mg/day SC in combination with ethinyl estradiol 0.1 µg/day SC, maintenance of pregnancy was comparable to intact control animals. Drospirenone effectively inhibited ovulation in mice and rats with half-maximal effects observed at subcutaneous doses of approximately 0.1 and 1 mg/day, respectively, and an oral

dose of 1 mg/day (rats). Following subcutaneous administration of drospirenone, a marked transformation of the endometrium was detected in castrated, infantile female rabbits, with a threshold dose of 100 to 300 µg/day. In vitro, drospirenone bound with high affinity to the progesterone receptor, and the binding affinity was not affected by the presence of ethinyl estradiol.

In addition to its progestational activity, drospirenone also has antiandrogenic activity. Oral or subcutaneous administration of drospirenone (0.3 to 10 mg/day for 7 days) dose dependently inhibited testosterone-induced growth of the seminal vesicle and prostate in castrated, testosterone-substituted rats. This activity does not appear to be centrally mediated in rats because decreases in the relative weights of male accessory sex organs occur in the absence of significant changes in testes weights or serum luteinizing hormone levels. Oral or subcutaneous administration of drospirenone (10 mg/day) to pregnant rats during the final trimester of pregnancy resulted in the feminization of male fetuses, characterized by a significant shortening of the anogenital distance and the length of the urethra.

Significant antimineralocorticoid activity, characterized by increased sodium excretion and an increase of the urinary Na⁺/K⁺ ratio, was observed following single oral or subcutaneous administration of drospirenone to adrenalectomized, aldosterone-substituted rats. Drospirenone was five to ten times more potent than spironolactone, and its aldosterone antagonist activity was not affected by concomitant administration of ethinyl estradiol. When administered for 21 days to ovariectomized female rats, drospirenone (10 mg/day) stimulated the Na⁺/K⁺ excretion ratio over the entire treatment period, while spironolactone (10 mg/day) became ineffective after the initial treatment phase due to counter-regulation. Drospirenone also exhibited significant antimineralocorticoid activity in vitro, inhibiting aldosterone-stimulated electrogenic sodium transport 10 times more effectively than either spironolactone or progesterone. In vitro, drospirenone binds with high affinity to the mineralocorticoid receptor.

Drospirenone has no androgenic activity. This was demonstrated in vitro by the lack of stimulation of androgen receptor-driven gene transcription. In vivo in castrated male rats, drospirenone (10 mg/day) did not stimulate the growth of accessory sex organs above castration level. The same dose had no virilizing effect on the process of sexual differentiation of female rat fetuses.

Drospirenone is devoid of estrogenic, gluco- and antiglucocorticoid activity, as concluded from the absence of an influence on vaginal epithelial cornification in rats, adrenal weight changes in rats, and thymus regression in adrenalectomized, glucocorticoid-substituted rats, respectively.

Drospirenone did not affect smooth muscle organs (ileum, trachea, uterus) in vivo (rabbit) or in vitro (guinea pigs). In female mice, drospirenone did not affect central nervous system function at single oral doses up to 100 mg/kg.

Pharmacokinetics

The pharmacokinetic characterization of the drug demonstrated that drospirenone is orally bioavailable in the laboratory animals which were used for toxicology studies. The qualitative

similarity in the profile of drug metabolites in the plasma of the test animals and human plasma further supports the adequacy of the test-species which were chosen. However, due to the much faster elimination of the drug, especially in rodents, it was necessary to administer high oral doses in order to achieve a systemic exposure to the parent drug comparable to or even exceeding human systemic exposure on the basis of plasma AUCs. Still, toxicokinetic investigations have shown that the high dose levels (≥ 10 mg/kg/day) which were used throughout the toxicology program and which represented a very high multiple of the oral human dose (≥ 170 -fold) also resulted in a substantial multiple of systemic exposure to the parent drug (ca 3-fold in mice, ca 10-fold in rats to >20 -fold in monkeys) relative to human exposure. The use of even higher doses would not have been appropriate because, for compounds like the contraceptive steroids, the toxic effects seen at highly exaggerated doses usually do not contribute useful information with regard to risk assessment for humans.

TOXICOLOGY

Acute Toxicity

Table 6 below summarizes the median lethal doses (LD₅₀) determined in acute toxicity studies with drospirenone.

Table 6: LD₅₀ Values for Drospirenone

Species	Doses Tested (mg/kg/day)	Route of Administration	LD ₅₀ (mg/kg)
Mouse	0, 250, 500, 1250, 2500	intragastric	500 - 2500
	0, 250, 500, 1250, 2500	intraperitoneal	250 - 500
Rat	0, 250, 500, 1250, 2000	intragastric	500 - 1250
	0, 100, 250, 500, 1250, 2000	intraperitoneal	100 - 250
Dog	0, 250	oral (capsules)	> 250
	0, 0.165	intravenous	> 0.165

The principle clinical signs observed in mice and rats were similar in all studies and included apathy, gait, and posture disturbances, and at higher doses, twitching, spasms, and/or unconsciousness. Deaths generally occurred within 3 to 4 days of dosing.

Single high doses of drospirenone to female Beagle dogs were generally well tolerated, with compound related effects limited to vomiting, transient changes in food/water consumption, and slight changes in serum biochemistry and coagulation parameters. No deaths occurred.

Long-term Toxicity

The long-term toxicity of drospirenone, alone and in combination with ethinyl estradiol and estradiol, was investigated after daily intragastric administration.

Compound related findings were generally limited to pharmacologic and exaggerated pharmacologic effects expected following administration of an exogenous progestogen or estrogen/progestogen combination. No organ toxicity was observed.

Changes observed following administration of drospirenone alone included:

- alterations in lipid, carbohydrate and protein metabolism (rats: ≥ 1 mg/kg/day)
- increased body weight gain and food consumption (rats: ≥ 3 mg/kg/day)
- decreased liver weights accompanied by decreased hepatic glycogen content (monkeys: ≥ 2 mg/kg/day)
- increased liver weights accompanied by increased hepatic DNA and protein content (rats: ≥ 50 mg/kg/day)
- changes in electrolyte excretion (rats: ≥ 10 mg/kg/day; monkeys: 10 mg/kg/day)
- decreased ovarian weights (mice: 30 mg/kg/day)
- decreased (mice: 30 mg/kg/day) or slightly increased (monkeys: 10 mg/kg/day) adrenal gland weights
- microscopic changes in endocrine target organs (mice: ≥ 3 mg/kg/day; rats: ≥ 3 mg/kg/day; monkeys: ≥ 0.2 mg/kg/day)

A spectrum of compound-related estrogenic, progestogenic and antimineralocorticoid effects was observed following administration of the combination to female mice, rats, and monkeys. In addition, the antagonism of some estrogenic effects (decreased body weight and food consumption (rats); hematologic changes (rats, monkeys); and increased uterine weights (mice)) and antagonism of some progestogenic effects (increased body weight and food consumption (rats)) were observed.

Synergism of other effects was observed in mice and rats and included atrophy of ovarian interstitial glands, decreased luteal mass and sexual cycles in mice, and decreased ovarian weights and increased hepatic N-demethylase activity in rats. In comparison with administration of either substance alone, administration of the combination to rats and cynomolgus monkeys eliminated some single substance effects (alterations in hepatic cytochrome P450 content). Overt toxicity was limited to one possible compound-related death in cynomolgus monkeys administered the combination at a dose of 3 mg/kg drospirenone +0.03 mg/kg ethinyl estradiol for 11 weeks.

Toxicokinetic monitoring showed that on the basis of $AUC_{(0-24h)}$ values, the highest doses used in mice (30 mg/kg/day), rats (15 mg/kg/day) and monkeys (10 mg/kg/day) which did not produce overt signs of toxicity led to roughly 10.6 times (mice), >12 times (rats) and ca 22 times (monkeys) higher systemic exposure as compared to human exposure at the therapeutic dose.

Carcinogenicity

The carcinogenic potential of drospirenone, alone and in combination with ethinyl estradiol, was investigated in female mice and rats after daily intragastric administration.

No carcinogenicity was observed after 2 years of treatment with drospirenone as a single compound in mice or rats. Mortality was increased in rats at the highest dose of drospirenone. The increased food intake of the rats with a resultant increase in body weight was considered as the reason for the reduction in their life span. In the mouse study, there were no effects on the survival of the animals observed after treatment with drospirenone.

Tumorigenic effects of the drug combination in mice were manifested by an increased incidence of pituitary adenomas at all doses, overall mammary tumors at the mid and low doses, and uterine adenocarcinomas at the mid and high doses in comparison with controls. The same qualitative tumor pattern (however, quantitatively more pronounced, especially in the pituitary) was seen in groups treated with ethinyl estradiol alone. As drospirenone alone elicited no tumorigenic response, the tumorigenic potential of the combination was attributed to ethinyl estradiol.

Treatment of rats with the drug combination resulted in an increased incidence of hepatic adenomas at the high dose and of total liver tumors from the mid dose onwards. A similar effect on liver tumor induction was seen in groups receiving ethinyl estradiol alone. Therefore, this effect in the livers could be attributed to the activity of ethinyl estradiol.

Compared to the control group, a tendency towards an increased rate of endometrial adenoma with a concomitant decrease in the rate of adenocarcinoma was seen in the uteri from the animals of the low-dose combination group. In the mid and high-dose combination groups, no endometrial adenomas or adenocarcinomas were noted, ie, there was a reduction in the rate of uterine tumors below the control level. A clear-cut increase in these uterine tumor incidences was induced by ethinyl estradiol when given alone from the mid dose onwards. Thus, the presence of drospirenone in the drug combination apparently led to a suppression of the deleterious estrogenic effect on the uterus. Treatment with ethinyl estradiol at the high dose led to an increased incidence of adenocarcinoma in the mammary glands. This effect was also completely counteracted by drospirenone in the drug combination group.

Evaluation of concomitant drug plasma concentrations revealed that exposure to drospirenone on the basis of $AUC_{(0-24h)}$ values amounted to roughly 0.1-, 0.5-, and 3-fold multiples of human exposure after the low, mid, and high doses, respectively. The corresponding exposure multiples for drospirenone in the rat were approximately 0.5, 3.5, and 10 to 12 times human steady-state exposure.

Mutagenicity

No mutagenic effect of drospirenone was demonstrated in vitro in bacterial (*Salmonella typhimurium*, *Escherichia coli*) or mammalian (human lymphocyte, Chinese hamster) cells in the presence or absence of extrinsic metabolic activation. Drospirenone did not increase the

occurrence of micronucleated red blood cells in vivo following single intragastric administration of 1 000 mg/kg to mice.

Drospirenone increased unscheduled DNA synthesis in primary hepatocytes of female rats in vitro in a dose-dependent manner at a concentration of 10 to 60 µg/mL. Intragastric administration of drospirenone 10 mg/kg/day to rats for 14 consecutive days generated 2 forms of DNA adducts in male and female rat livers. Low levels of three compound-related DNA adducts were also observed in the livers of female mice given drospirenone 10 mg/kg/day, alone or in combination with 0.1 mg/kg/day ethinyl estradiol in the carcinogenicity study. In contrast to these findings observed in rodent livers, results from an in vitro study conducted with drospirenone 5 µg/mL in human liver slices did not indicate a DNA adduct-forming potential of drospirenone in human tissue. Given the lack of any drospirenone-related liver tumor formation in mice and rats, the biological relevance of this interaction with DNA in the rodent liver with regard to risk assessment in humans is questionable.

Reproduction and Teratology

The reproductive toxicity of drospirenone, alone and in combination with ethinyl estradiol, was investigated in rats, rabbits, and monkeys following intragastric administration.

As expected from the pharmacological activity of an estrogen/progestogen combination, estrous cycle disturbances and a transient impairment of fertility were observed in rats when treated for 6 weeks prior to mating with doses of 5 mg/kg/day drospirenone + 0.05 mg/kg/day ethinyl estradiol and higher. Pre- and postimplantation losses were significantly increased when 10 mg/kg/day drospirenone + 0.1 mg/kg/day ethinyl estradiol were administered during the preimplantation phase of gestation in rats.

No teratogenicity was observed following intragastric administration of drospirenone, alone or in combination with ethinyl estradiol, to female rats, rabbits and/or monkeys prior to mating or during gestation. Compound related maternal toxicity, characterized by decreased body weight gain (rats) and occasional vomiting (monkeys), was observed. The incidence of abortions was increased following administration of high doses of drospirenone (100 mg/kg/day) to pregnant rabbits, and a dose-dependent increase in abortions occurred following the administration of all doses to monkeys. Embryotoxicity and slight retardations of fetal development (eg, delayed ossification of feet bones, sternebrae, vertebrae; incomplete ossification of skull; slight increase in visceral abnormalities) were observed in the rat and rabbit at drospirenone doses of 15 mg/kg/day and 100 mg/kg/day, respectively.

Virilization of female fetuses (attributed to ethinyl estradiol) and feminization of male fetuses (attributed to drospirenone) were observed following administration of the drug combination to pregnant rats on days 14 through 21 of pregnancy, beginning at doses of 5+0.05 mg/kg and 15+0.15 mg/kg, respectively. If exposure estimates from nonpregnant rats are extrapolated to pregnant animals, the administration of 15 mg/kg/day drospirenone would result in plasma exposure levels which are at least 10 times higher than the steady-state human exposure after intake of ANGELIQ.

Prolonged or incomplete parturition or inability to deliver was observed when the drug combination was administered to rats from day 15 of gestation through day 3 postpartum. In the rat peri-/postnatal study, treatment from days 15 to 18 of gestation and days 1 to 22 postpartum caused a dose-dependent delay in postnatal development (body weight, physical and functional parameters) and a dose-dependent increased mortality of the F1 offspring. These observations were attributed to the negative effects of drospirenone and/or ethinyl estradiol on lactogenesis and milk secretion.

A reduced reproductive performance of the F1 animals was observed at the dose of 45 mg/kg/day drospirenone + 0.45 mg/kg/day ethinyl estradiol. This was attributed to an impairment of sex organ development in the male offspring due to the antiandrogenic activity of drospirenone.

REFERENCES

1. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *Jama*. 2004 Apr 14;291(14):1701-12.
2. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *Jama*. 2003 Jun 25;289(24):3243-53.
3. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama*. 2002 Jul 17;288(3):321-33.
4. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *Jama*. 2002 Jul 3;288(1):49-57.
5. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *Jama*. 1998 Aug 19;280(7):605-13.
6. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *Jama*. 2004 Jun 23;291(24):2947-58.
7. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *Jama*. 2003 May 28;289(20):2651-62.

8. Archer DF, Thorneycroft IH, Foegh M, Hanes V, Glant MD, Bitterman P, et al. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. *Menopause*. 2005 Nov-Dec;12(6):716-27.
9. Binkley KE, Davis A, 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol*. 2000 Sep;106(3):546-50.
10. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med*. 2003 Mar;114(4):294-8.
11. Fuhrmann U, Krattenmacher R, Slater EP, Fritzemeier KH. The novel progestin drospirenone and its natural counterpart progesterone: biochemical profile and antiandrogenic potential. *Contraception*. 1996 Oct;54(4):243-51.
12. Losert W, Casals-Stenzel J, Buse M. Progestogens with antimineralocorticoid activity. *Arzneimittelforschung*. 1985;35(2):459-71.
13. Muhn P, Fuhrmann U, Fritzemeier KH, Krattenmacher R, Schillinger E. Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. *Ann N Y Acad Sci*. 1995 Jun 12;761:311-35.
14. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med*. 2001 Nov 12;161(20):2417-29.
15. Oelkers W, Berger V, Bolik A, Bahr V, Hazard B, Beier S, et al. Dihydrospirorenone, a new progestogen with antimineralocorticoid activity: effects on ovulation, electrolyte excretion, and the renin-aldosterone system in normal women. *J Clin Endocrinol Metab*. 1991 Oct;73(4):837-42.
16. Paterson ME, Wade-Evans T, Sturdee DW, Thom MH, Studd JW. Endometrial disease after treatment with oestrogens and progestogens in the climacteric. *Br Med J*. 1980 Mar 22;280(6217):822-4.
17. Pollow K, Juchem M, Elger W, Jacobi N, Hoffmann G, Mobus V. Dihydrospirorenone (ZK30595): a novel synthetic progestagen--characterization of binding to different receptor proteins. *Contraception*. 1992 Dec;46(6):561-74.
18. Schurmann R, Holler T, Benda N. Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric*. 2004 Jun;7(2):189-96.
19. Warming L, Ravn P, Nielsen T, Christiansen C. Safety and efficacy of drospirenone used in a continuous combination with 17beta-estradiol for prevention of postmenopausal osteoporosis. *Climacteric*. 2004 Mar;7(1):103-11.

20. Whitehead MI, King RJ, McQueen J, Campbell S. Endometrial histology and biochemistry in climacteric women during oestrogen and oestrogen/progestogen therapy. J R Soc Med. 1979 May;72(5):322-7.
21. Report No. AU18: An open-label, randomized, multicenter study to investigate safety and efficacy of 2 continuously combined estradiol/drospirenone preparations compared to Premique/Premelle when used for hormone replacement therapy over 2 years in postmenopausal women. Data on file.

PART III: CONSUMER INFORMATION

Pr **ANGELIQ®**

Drospirenone and estradiol-17 β tablets

This leaflet is Part III of a three-part "Product Monograph" published when ANGELIQ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ANGELIQ. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ANGELIQ is approved for use in postmenopausal women with an intact uterus:

- to reduce and relieve vasomotor symptoms (hot flashes and night sweats)
- to treat moderate and severe dryness, itching, and burning in and around the vagina associated with menopause

ANGELIQ should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear, and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests. Unexpected or undiagnosed vaginal bleeding should be investigated by your doctor.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor.

You and your healthcare provider should talk regularly about whether you still need treatment with ANGELIQ to control these problems.

If you have had a hysterectomy (surgical removal of the uterus), endometrial hyperplasia cannot occur and administration of a progestin is not necessary. Therefore, ANGELIQ **should not** be used by women who have had a hysterectomy.

What it does:

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your health care provider should talk regularly about whether you still need treatment with ANGELIQ.

The estradiol in ANGELIQ not only relieves your menopausal symptoms, but, like estrogens produced by your body, may also stimulate growth of the inner lining of the uterus, the endometrium. In menopausal and postmenopausal women with an intact uterus, stimulation of growth of the endometrium may result in irregular bleeding. In some cases this may progress into a disorder of the uterus known as endometrial hyperplasia (overgrowth of the lining of the uterus). Endometrial hyperplasia increases the risk of endometrial cancer (cancer of the lining of the uterus). The risk of endometrial hyperplasia is reduced if a progestin is given together with estrogen replacement therapy.

When it should not be used:

You **should not** use ANGELIQ if you:

- have active liver disease
- have a personal history of breast cancer or endometrial cancer (cancer of the lining of the uterus)
- have or have had liver tumors
- have severe kidney disease
- have a very high level of fatty acids in the blood called hypertriglyceridemia
- have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus)
- have experienced undiagnosed or abnormal genital bleeding
- have a history of heart attack, heart disease, or stroke
- experience migraine headaches
- have a personal history of blood clots or active thrombophlebitis (inflammation of the veins)
- are at high risk of having a blood clot including if you were born with certain blood clotting abnormalities

- have had partial or complete loss of vision due to blood vessel disease of the eye
- are pregnant or think you may be pregnant. (Since pregnancy may be possible early in menopause while you are still having spontaneous periods, the use of nonhormonal birth control should be discussed with your doctor at this time. If you take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.)
- are breast feeding
- have had a hysterectomy (surgical removal of the uterus)
- have had an allergic or unusual reaction to estrogen, progestin, or any component of ANGELIQ
- have adrenal disease

What the medicinal ingredients are:

Drospirenone and estradiol-17 β

What the nonmedicinal ingredients are:

Corn starch, ferric oxide pigment, hydroxypropylmethyl cellulose, lactose monohydrate, macrogol, magnesium stearate, modified starch, povidone, talc, and titanium dioxide.

What dosage forms it comes in:

ANGELIQ (drospirenone and estradiol-17 β) is available in a 28-day regimen. Each blister pack contains 28 dark pink film-coated tablets. Each tablet contains 1 mg drospirenone and 1 mg estradiol-17 β .

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs), and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke, and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at **the lowest effective dose and for the shortest period of time** possible. Regular medical follow-up is advised.

Breast Cancer

The results of the WHI trial indicated an increased risk of breast cancer in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo. The results of the WHI trial indicated no difference in the risk of breast cancer in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies, or abnormal mammograms (breast x-rays) should consult with their doctor before starting hormone replacement therapy.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review technique for breast self-examination with your doctor.

Ovarian Cancer

In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

Overgrowth of the lining of the uterus and cancer of the uterus

The use of *estrogen-alone* therapy by postmenopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus). The purpose of adding a progestin medication to estrogen therapy is to reduce the risk of endometrial hyperplasia.

You should discuss risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

Heart Disease and Stroke

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Abnormal Blood Clotting

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke, or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Gallbladder Disease

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

Dementia

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in postmenopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

Certain medical conditions may be aggravated by estrogens or progestins. Therefore, these hormones should either not be used at all or should be used with caution under these conditions.

BEFORE you use ANGELIQ talk to your doctor or pharmacist if you:

- are taking any other prescription or nonprescription medications (including herbal products such as St. John's wort). There are some medicines which may interfere with the effects of ANGELIQ and ANGELIQ may interfere with the effects of other medicines.
- are currently on daily, long-term treatment for a chronic condition with any of the medications listed below:
 - nonsteroidal anti-inflammatory drugs (NSAIDs) when taken long-term and for the treatment of arthritis or other problems (eg, ibuprofen, naproxen, or others)
 - potassium-sparing diuretics (spironolactone and others)
 - potassium supplements
 - Angiotensin converting enzyme (ACE) inhibitors and Angiotensin-II receptor antagonists for the treatment of high blood pressure (eg, captopril, enalapril, lisinopril, losartan, valsartan, irbesartan, or others)
 - heparin
- have a history of allergy or intolerance to any medications or other substances

- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of endometrial hyperplasia (overgrowth of the lining of the uterus)
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- drink alcohol
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- if you are undergoing surgery or need long bed rest
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have been diagnosed with high prolactin levels or prolactinoma
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- are breast feeding
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have a history of depression
- have been told that you have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract
- have been diagnosed with hearing loss due to otosclerosis
- have been diagnosed with lupus

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ANGELIQ include:

- anticoagulants, antidiabetic agents
- drugs used for the treatment of certain heart diseases or high blood pressure (eg, diltiazem, verapamil)
- drugs used for the treatment of HIV infections and Hepatitis C Virus infections (e.g., nelfinavir, ritonavir, ritonavir-boosted protease inhibitors, boceprevir, telaprevir, nevirapine)
- barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, primidone, phenytoin, oxcarbazepine, topiramate, felbamate or rifamicin
- antibiotics (eg, erythromycin, clarithromycin, penicillin, tetracycline)
- antifungals (eg, griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole)
- antivirals (ritonavir)

Alcohol, grapefruit juice, and St. John's wort may also interact with ANGELIQ.

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins, or herbal products.

PROPER USE OF THIS MEDICATION

Usual dose

ANGELIQ is very simple to take – one pill, once a day, every day. You can take ANGELIQ any time of day, with or without food. However, it's usually easier to plan to take it at the same time each day.

Estrogens should be used only as long as needed. You and your doctor should talk regularly about whether you still need treatment with ANGELIQ.

Overdose

Symptoms: Overdosage with estrogen or progestin containing products may cause nausea, breast discomfort, fluid retention, bloating, vaginal bleeding, depressed mood, tiredness, acne, and hirsutism (excessive hair growth).

In case of drug overdose, contact health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose

If you forget a tablet, take it as soon as you remember and take the next one at your regular time. If you have missed your tablet by more than 24 hours, leave the tablet in the pack and take the next one at the regular time. Do not take a double dose to make up for a missed one. If you forget several tablets, you may get some slight vaginal bleeding or spotting.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

During treatment you may experience some vaginal bleeding at unexpected times (breakthrough bleeding and spotting). These symptoms normally lessen with continued treatment. If they don't, contact your doctor. About one in five women using ANGELIQ experience breast pain.

Women who have used ANGELIQ have reported the side effects listed below. The reported side effects have been divided into groups, depending on how commonly they occurred.

Common effects (may affect up to 1 in 10 users)

- abdominal pain or bloating, or pain in your fingers or toes
- feeling sick (nausea) or feeling unusually tired or weak
- headache, mood swings, hot flashes, nervousness
- enlarged or lumpy breasts
- increased size of fibroids in the womb (uterus)
- growth of cells at the neck of the womb
- vaginal discharge
- breakthrough bleeding
- depression

Uncommon effects (may affect up to 1 in 100 users)

- back, pelvic, chest or joint pain
- migraine, high blood pressure, fast or irregular heartbeats (palpitations), varicose veins, blood clots in the veins, inflammation of veins usually in the legs, widening of blood vessels (which may make you feel faint)
- stomach or intestinal problems, diarrhea, constipation, vomiting, flatulence, increased appetite, change in laboratory tests
- fluid retention leading to swelling of parts of the body, increase or decrease in weight
- high levels of fat in the blood
- muscle cramps
- difficulty sleeping, dizziness, decreased sex drive, difficulty concentrating, pins and needles, increased sweating, anxiety, dry mouth, spinning sensation (vertigo)

- difficulty breathing
- unusual hair loss or hair growth, skin problems, a feeling of fullness and tenderness in the breasts, breast cancer
- changes to your sense of taste
- vaginal infections, womb and neck of the womb (cervix) problems, painful periods, fluid filled sacs in the ovaries (ovarian cysts), urinary tract infections, loss of bladder or bowel control
- abnormal vision

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain, nausea or vomiting		✓	
	Breast lump		✓	
	Persistent sad mood			✓
	Unexpected vaginal bleeding		✓	
Uncommon	Vomiting		✓	
	Pain or swelling in the leg			✓
Rare	Crushing chest pain or chest heaviness			✓
	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
	Sudden partial or complete loss of vision			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
	Yellowing of the skin or eyes (jaundice)			✓

This is not a complete list of side effects. For any unexpected effects while taking ANGELIQ, contact your doctor or pharmacist.

HOW TO STORE IT

ANGELIQ tablets should be stored at room temperature, between 15°C and 30°C. Do not refrigerate or freeze. Please note the expiry date on the pack. Do not use after this date.

ANGELIQ should be kept out of the reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the manufacturer at the above-mentioned phone number and email address.

This leaflet was prepared by:



Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario L4W 5R6
Canada

Last revised: February 17, 2016

© 2016, Bayer Inc.

® TM see www.bayer.ca/tm-mc