PRODUCT MONOGRAPH

[Pr]Drospirenone and Ethinyl Estradiol Tablets USP

3 mg drospirenone and 0.02 mg ethinyl estradiol tablets

Oral Contraceptive

Acne Therapy

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Drospirenone and Ethinyl Estradiol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet / 3 mg drospirenone and 0.02 mg ethinyl estradiol	Lactose monohydrate *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

Drospirenone and Ethinyl Estradiol Tablets USP are indicated for:

- Conception control
- Treatment of moderate acne vulgaris in women ≥14 years of age who have no known contraindications to oral contraceptive therapy, desire contraception, and have achieved menarche

CONTRAINDICATIONS

Drospirenone and Ethinyl Estradiol Tablets USP should not be used in women with:

- a history of or actual thrombophlebitis or thromboembolic disorders
- a history of or actual cerebrovascular disorders
- a history of or actual myocardial infarction or coronary artery disease
- valvular heart disease with complications
- a history of or actual prodromi of a thrombosis (eg, transient ischemic attack, angina pectoris)
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  - severe hypertension (persistent values of ≥160/100 mmHg)
  - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - severe dyslipoproteinemia
  - smoking, if over age 35
  - diabetes mellitus with vascular involvement
  - major surgery associated with an increased risk of postoperative thromboembolism
  - prolonged immobilization

- use with the Hepatitis C virus combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see **WARNINGS AND PRECAUTIONS**)
- active liver disease or history of or actual benign or malignant liver tumors
- known or suspected carcinoma of the breast
- carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- undiagnosed abnormal vaginal bleeding
- steroid-dependent jaundice, cholestatic jaundice, history of jaundice in pregnancy
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields
- known or suspected pregnancy
- current or history of migraine with focal aura
- history of or actual pancreatitis if associated with severe hypertriglyceridemia
- renal insufficiency
- hepatic dysfunction
- adrenal insufficiency
- hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptive, including Drospirenone and Ethinyl Estradiol Tablets USP, should not be used by women who are over 35 years of age and smoke. Women should be counselled not to smoke (see **WARNINGS AND PRECAUTIONS** – **Cardiovascular** section below).

Hormonal contraceptives **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. While using hormonal contraceptives, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** hormonal contraceptives to protect against STIs.

General

Discontinue Medication at the Earliest Manifestation of:

A. Thromboembolic and Cardiovascular Disorders such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.

B. Conditions that Predispose to Venous Stasis and to Vascular Thrombosis

(eg, immobilization after accidents or confinement to bed during long-term illness). Other nonhormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **WARNINGS AND PRECAUTIONS** – **Peri-operative Considerations**.

C. Visual Defects - Partial or Complete

D. Papilledema, or Ophthalmic Vascular Lesions

E. Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache

F. Increase in Epileptic Seizures

The following information is provided from studies of combination oral contraceptives (COCs).

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity, and diabetes. Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus (1), hemolytic uremic syndrome (2-4), chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) (5), sickle cell disease (6), valvular heart disease and atrial fibrillation (7, 8).

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established:
porphyria, (9) systemic lupus erythematosus, (10) hemolytic uremic syndrome, (11) Sydenham's chorea, (12, 13) herpes gestationis, (14, 15) and otosclerosis-related hearing loss. (16)

The information contained in this section is principally from studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered orally remains to be determined.

Drospirenone and Ethinyl Estradiol Tablets USP contains 3 mg of the progestin drospirenone (DRSP) that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Drospirenone and Ethinyl Estradiol Tablets USP should not be used in patients with conditions that predispose to hyperkalemia (eg, renal insufficiency, hepatic dysfunction, and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.

<u>Carcinogenesis and Mutagenesis</u>

Malignancies may be life-threatening or may have a fatal outcome.

Breast Cancer

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age, the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity, and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than eight years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

Women receiving oral contraceptives should be instructed in self-examination of their breasts.
Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended, because, if breast cancer should develop, drugs that contain estrogen may cause a rapid progression.

Cervical Cancer

The most important risk factor for cervical cancer is persistent human papillomavirus infection (HPV). Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk, but there continues to be controversy about the extent to which this finding is attributable to confounding effects, eg, cervical screening and sexual behaviour including use of barrier contraceptives.

Hepatocellular Carcinoma

Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use. However, the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is extremely small. A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement, or signs of intra-abdominal hemorrhage occur in women taking COCs.

See **TOXICOLOGY** for discussion of animal data.

Cardiovascular

Predisposing Factors for Coronary Artery Disease
Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, particularly in women over 35 years of age, and with the number of cigarettes smoked. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke. For this reason, combination oral contraceptives, including Drospirenone and Ethinyl Estradiol Tablets USP, should not be used by women who are over 35 years of age and smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether oral contraceptives accentuate this risk is unclear.

In low-risk, nonsmoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Hypertension
Patients with essential hypertension whose blood pressure is well-controlled may be given hormonal contraceptives, but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary. An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use.

Endocrine and Metabolism

Diabetes

Current low-dose oral contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes should be monitored more frequently while using oral contraceptives.

Lipid and Other Metabolic Effects

A small proportion of women will have adverse lipid changes while on oral contraceptives. Alternative contraception should be used in women with uncontrolled dyslipidemia (see also **CONTRAINDICATIONS**). Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Gastrointestinal

Published epidemiological studies indicate a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established. (17-22)

Genitourinary

Vaginal Bleeding
Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Fibroids
Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of oral contraceptives.

Hematologic

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism, and of cerebrovascular accidents. These events occur rarely.

The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive or restarts (following a 4-week or greater pill-free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months. VTE is life-threatening and is fatal in 1% to 2% of cases. (23)

A large, prospective 3-armed cohort study has shown that the frequency of VTE diagnosis ranges from about 8 to 10 per 10,000 woman-years in users of oral contraceptives with low estrogen content (<50 mcg ethinyl estradiol). The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman-years in nonpregnant, non-COC users and ranges from 20 to 30 per 10,000 woman-years in pregnant women or postpartum.

Overall the risk for VTE in users of oral contraceptives with low estrogen content (<50 mcg ethinyl estradiol) is 2- to 3-fold higher than for nonusers of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

Several epidemiological studies have examined the risk of VTE with drospirenone-containing COCs versus other COCs. Two prospective cohort studies showed that the risk of VTE with drospirenone-containing COCs is comparable to that of other COCs, including levonorgestrel-containing COCs. (24, 25) One case-control and three retrospective cohort studies suggested that the risk of VTE with drospirenone-containing COCs is higher compared to users of levonorgestrel-containing COCs. (26-29) Two additional nested case-control studies have reported a two-fold and three-fold increased risk of idiopathic VTE in users of drospirenone-containing COCs as compared with levonorgestrel-containing COCs. (30, 31) These retrospective studies suggest a potential 1.5-3 times risk of VTE in users of drospirenone-containing COCs. Epidemiological studies have inherent methodological issues making the interpretation of their results complex. (26-31) However, prescribers should consider the benefits and risks for specific patients with respect to VTE risk given the current retrospective epidemiological studies suggesting a higher risk of VTE with drospirenone-containing COCs compared to levonorgestrel-containing COCs.

VTE, manifesting as deep venous thrombosis (DVT) and/or pulmonary embolism (PE), may occur during the use of all COCs.

Extremely rarely, thrombosis has been reported to occur in other blood vessels (eg, hepatic, mesenteric, renal, cerebral, or retinal veins and arteries) in COC users.

Symptoms of DVT can include: Unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg, which may be felt only when standing or walking; increased warmth in the affected leg; red or discolored skin on the leg.

Symptoms of PE can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (eg, "shortness of breath", "coughing") are nonspecific and might be misinterpreted as more common or less severe events (eg, respiratory tract infections).

The risk for arterial thromboembolism (ATE) in users of oral contraceptives with low estrogen content (<50 mcg ethinyl estradiol) ranges from about 1 to 3 cases per 10,000 woman-years. An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion, or myocardial infarction (MI). Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling, and slight blue discoloration of an extremity; acute abdomen.

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting, or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events are life-threatening and may have a fatal outcome.

Other Risk Factors for Venous or Arterial Thromboembolism or of a Cerebrovascular Accident

Other generalized risk factors for venous or arterial thromboembolism include but are not limited to age, severe obesity (body mass index >30 kg/m^2), a personal history, a positive family history (the occurrence of VTE/ATE in a direct relative at a relatively early age may indicate genetic predisposition) and systemic lupus erythematosus. If a hereditary or acquired predisposition for venous or arterial thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any COC use. The risk of VTE/ATE may be temporarily increased with prolonged immobilization, major surgery, or trauma. In these situations, it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume COC use until two weeks after complete remobilization. Also, patients with varicose veins and leg cast should be closely supervised. Other risk factors may include smoking (with heavier smoking and increasing age, the risk further increases, especially in women over 35 years of age), dyslipoproteinemia, hypertension, migraine, valvular heart disease, and atrial fibrillation.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinyl estradiol).

Hepatic/Biliary/Pancreatic

In some cases of elevated liver enzymes reported during clinical trials with drospirenone and ethinyl estradiol, a contributory role of drospirenone and ethinyl estradiol tablets could not be ruled out. Drospirenone and Ethinyl Estradiol Tablets USP are contraindicated in patients with active liver disease (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS – Drug-Laboratory Test Interactions**).

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

Jaundice

Patients who have had jaundice should be given oral contraceptives with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use.

The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If a patient develops jaundice that proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking hormonal contraceptives, changes in the composition of the bile may occur, and an increased incidence of gallstones has been reported.

Gallbladder Disease

Patients taking oral contraceptives have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after 4 or 5 years.

Hepatic Nodules

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Hepatitis C

Drospirenone and Ethinyl Estradiol Tablets USP must be discontinued prior to starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**). During clinical trials with ombitasvir, paritaprevir, ritonavir, with and without dasabuvir, ALT elevations 5 to >20 times the upper limit of normal (ULN) were significantly more frequent in healthy female subjects and HCV infected women using ethinyl estradiol-containing medications such as COCs. Drospirenone and Ethinyl Estradiol Tablets USP can be restarted approximately 2 weeks following completion of treatment with the HCV combination drug regimen.

Immune

Angioedema
Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular, in women with hereditary angioedema. (32-34)

Neurologic

Migraine and Headache
The onset or exacerbation of migraine or the development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of hormonal contraceptives and evaluation of the cause. Women with migraine headaches who take oral contraceptives may be at increased risk of stroke (see **CONTRAINDICATIONS**).

Ophthalmologic

Ocular Disease
Patients who are pregnant or are taking oral contraceptives may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised.

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

Peri-operative Considerations

There is an increased risk of thromboembolic complications in oral contraceptive users after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least 1 month prior to **MAJOR** elective surgery. Oral contraceptive use should not be resumed until the first menstrual period after hospital discharge following surgery.

Psychiatric

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made, which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

Renal

Fluid Retention
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution and only with careful monitoring in patients with conditions which might be aggravated by fluid retention.

Sexual Function/Reproduction

Return to Fertility
After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least 1 normal spontaneous menstrual cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

Amenorrhea
In some women, withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to directions prior to the first missed withdrawal bleed, or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

Reduced Efficacy
The efficacy of COCs may be reduced in the event of missed tablets, gastrointestinal disturbances or concomitant medication (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

Skin
Chloasma may occasionally occur with use of COCs, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

Special Populations

Pregnant Women
Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with Drospirenone and Ethinyl Estradiol Tablets USP, further intake must be stopped. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child. One infant was born with esophageal atresia during treatment with drospirenone and ethinyl estradiol tablets (3 mg drospirenone and 0.03 mg ethinyl estradiol), an OC of similar composition but with different dose and regimen. The causal association is unknown.

Nursing Women
In breast-feeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low-dose oral contraceptives are harmful to the nursing infant.

If possible, the nursing mother should be advised not to use oral contraceptives, but to use other forms of contraception, until she has completely weaned her child.

After oral administration of drospirenone and ethinyl estradiol tablets (3 mg drospirenone and 0.03 mg ethinyl estradiol), an OC of similar composition but with different dose and regimen, about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

Pediatrics
The safety and efficacy of drospirenone and ethinyl estradiol have not been established in women under the age of 14 years. Use of this product before menarche is not indicated.

Geriatrics
Drospirenone and Ethinyl Estradiol Tablets USP is not indicated for use in postmenopausal women.

Monitoring and Laboratory Tests

Physical Examination and Follow-up
Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (eg, deep vein thrombosis, stroke, myocardial infarction) at a young age. Breasts, liver, extremities, and pelvic organs should be examined, and a Papanicolaou (PAP) smear should be taken if the patient has been sexually active.

The first follow-up visit should be done 3 months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives:

- arterial and venous thromboembolism
- being diagnosed with breast cancer

- benign and malignant hepatic tumors
- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension
- mesenteric thrombosis
- myocardial infarction
- neuro-ocular lesions (eg, retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

The following adverse reactions also have been reported in patients receiving oral contraceptives: nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10% or fewer of patients during the first cycle. The following other reactions, as a general rule, are seen less frequently or only occasionally:

- abdominal pain
- amenorrhea during and after treatment
- angioedema (exogenous estrogens may induce or exacerbate symptoms of angioedema in women with hereditary angioedema)
- auditory disturbances
- breakthrough bleeding
- breast changes (tenderness, enlargement, and secretion)
- cataracts
- changes in appetite
- change in corneal curvature (steepening)
- changes in libido
- change in menstrual flow
- change in weight (increase or decrease)
- changes in glucose tolerance or effect on peripheral insulin resistance
- chloasma or melasma which may persist
- cholestatic jaundice
- chorea
- Crohn's disease
- cystitis-like syndrome
- mental depression
- diarrhea
- dizziness
- dysmenorrhea
- edema
- endocervical hyperplasia
- erythema multiforme
- erythema nodosum

- gallstone formation[a]
- gastrointestinal symptoms (such as abdominal cramps and bloating)
- headache
- hemolytic uremic syndrome[a]
- hemorrhagic eruption
- herpes gestationis[a]
- hirsutism
- hypersensitivity
- hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- hypertension
- impaired renal function
- increase in size of uterine leiomyomata
- intolerance to contact lenses
- jaundice related to cholestatis[a]
- liver function disturbances
- loss of scalp hair
- migraine
- nervousness
- optic neuritis
- otosclerosis-related hearing loss[a]
- pancreatitis
- porphyria[a]
- possible diminution in lactation when given immediately postpartum
- premenstrual-like syndrome
- pruritis related to cholestasis[a]
- rash (allergic)
- Raynaud's phenomenon
- reduced tolerance to carbohydrates
- retinal thrombosis
- rhinitis
- spotting
- Sydenham's chorea[a]
- systemic lupus erythematosus[a]
- temporary infertility after discontinuation of treatment
- urticaria
- ulcerative colitis
- vaginal candidiasis
- vaginal discharge
- vaginitis

[a] Occurrence or deterioration of conditions for which association with COC use is not conclusive.

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

The clinical development programs were conducted independently for each of the 2 indications and utilized indication-specific inclusion criteria, study designs, and settings. Thus, the safety results of the studies are presented separately and are not pooled.

The following adverse drug reactions were reported at a frequency ≥ 1% in pivotal clinical trials using drospirenone and ethinyl estradiol as an oral contraceptive:

Table 2: Adverse Drug Reactions With Frequency of ≥1% in Pivotal OC Clinical Trials With Drospirenone and Ethinyl Estradiol (N=2438)

HARTS Body System	HARTS Preferred Term	n	%
Digestive System/General	Nausea	48	2.0
Nervous System/General	Headache	118	4.8
Nervous System/Central Nervous System/Brain	Emotional lability	28	1.1
Skin and Appendages/Dermatose/Acneform	Acne	24	1.0
Skin and Appendages/Breast Disorders	Breast pain	106	4.3
Urogenital System/Female Genital Disorders/Menstrual Disorders	Amenorrhea	61	2.5
	Intermenstrual bleeding	110	4.5

Abbreviations: HARTS = Hoechst Adverse Reaction Terminology System, N = total number, n = number of subjects, OC = oral contraception

The following adverse drug reactions were reported at a frequency ≥1% in pivotal clinical trials using drospirenone and ethinyl estradiol in the treatment of moderate acne vulgaris:

Table 3: Adverse Drug Reactions With Frequency of ≥1% in Pivotal Moderate Acne Vulgaris Clinical Trials With Drospirenone and Ethinyl Estradiol (N=536)

HARTS Body System	HARTS Preferred Term	n	%
Digestive System/General	Nausea	22	4.1
	Vomiting	7	1.3
Nervous System/General	Headache	24	4.5
Nervous System/Central Nervous System/Brain	Emotional lability	12	2.2
	Depression	7	1.3
Skin and Appendages/Breast Disorders	Breast pain	8	1.5
Urogenital System/Female Genital Disorders/Menstrual Disorders	Dysmenorrhea	8	1.5
	Metrorrhagia	53	9.9
	Menorrhagia	14	2.6
	Menstrual Disorder	8	1.5

Abbreviations: HARTS = Hoechst Adverse Reaction Terminology System, N = total number, n = number of subjects

Less Common Clinical Trial Adverse Drug Reactions

The following adverse drug reactions were seen at a frequency of <1% and ≥0.1% in pivotal clinical trials using drospirenone and ethinyl estradiol as an oral contraceptive:

Body as a whole: abdominal pain, asthenia, back pain, pain in extremity, pelvic pain

Cardiovascular system: hypertension, migraine, varicose vein

Digestive system: diarrhea, dyspepsia, flatulence, gastritis, vomiting

Metabolic and nutritional disorders: weight gain, edema, peripheral edema

Musculoskeletal system: muscle cramps

Nervous system: dizziness, paresthesia, sweating increased, depression, libido decreased, nervousness, somnolence

Skin and appendages: breast enlargement, acne, pruritus, fibrocystic breast, rash

Urogenital system: hypomenorrhea, leukorrhea, vaginal dryness, vaginal moniliasis, dysmenorrhea, metrorrhagia, vaginal hemorrhage, menstrual disorder, PAP smear suspicious, vaginitis, menorrhagia

The following adverse drug reactions were seen at a frequency of <1% and ≥0.1% in pivotal clinical trials using drospirenone and ethinyl estradiol in the treatment of moderate acne vulgaris:

Body as a whole: abdominal pain, asthenia, malaise

Cardiovascular system: hypertension, migraine

Urogenital system: amenorrhea, leukorrhea, PAP smear suspicious, uterine enlargement, vaginal moniliasis

The following adverse drug reactions were seen at a frequency of <0.1% and ≥0.01% in pivotal clinical trials using drospirenone and ethinyl estradiol as an oral contraceptive:

Body as a whole: abdomen enlarged, accidental injury, allergic reaction, cyst, face edema, hernia, infection, moniliasis

Cardiovascular system: phlebitis, syncope, tachycardia, vascular disorder

Digestive system: biliary pain, cholecystitis, constipation, gastrointestinal disorder, gastrointestinal fullness, increased appetite, liver function test abnormal, oral moniliasis

Endocrine system: endocrine disorder

Metabolic and nutritional disorders: generalized edema, SGPT increased, weight loss,

Nervous system: hot flashes, insomnia, vertigo

Respiratory system: epistaxis

Skin and appendages: alopecia, breast neoplasm, chloasma, dermatitis acneiform, dry skin, eczema, erythema nodosum, hypertrichosis, skin disorder, skin striae

Special senses: conjunctivitis, dry eye, eye disorder

Urogenital system: anorgasmia, cervix neoplasm, dyspareunia, endometrial disorder, ovarian cyst, vulvovaginitis, withdrawal bleeding

Postmarket Adverse Drug Reactions

The following unexpected adverse events have also been reported very rarely in users of drospirenone and ethinyl estradiol, but a causal relationship has not been established: hot/cold sensations, muscle spasms, muscle twitching, and erythema multiforme

In addition, 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) have been identified as Adverse Drug Reactions (ADRs) from postmarketing experience reported in association with the use of drospirenone and ethinyl estradiol (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Hematologic**). Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may lead to breakthrough bleeding and/or may result in an altered response to either agent (see Table 4 and Table 5). Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and nonprescription, before oral contraceptives are prescribed.

Drug-Drug Interactions

Table 4 – Drugs Which May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins	Dose 2 hours apart.

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antibiotics (35)	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.
	Rifabutin Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism	Use another non-hormonal method of contraception.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.
	Troleandomycin	May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice.	
Anticonvulsants (36-38)	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 mcg ethinyl estradiol), another drug, or another non-hormonal method of contraception.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur	Use another non-hormonal method of contraception.
Cholesterol lowering agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy	Use another non-hormonal method of contraception.
HCV Protease Inhibitors	Boceprevir Telaprevir	Remains to be confirmed	Use another drug or another non-hormonal method of contraception.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes	Use another drug or another non-hormonal method of contraception.
Non-nucleoside reverse transcriptase inhibitors (39, 40)	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Sedatives and Hypnotics	Barbiturates Benzodiazepines Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes	For short course, use additional non-hormonal method of contraception or another drug. For long course, use another non-hormonal method of

Class of Compound	Drug	Proposed Mechanism	Suggested Management
			contraception or higher dose oral contraceptives.
Other Drugs	Analgesics Antihistamines Antimigraine preparations Phenylbutazone preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed	

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Women on short-term treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing light pink film-coated tablets in the COC pack, the hormone-free white film-coated tablets should be omitted and the next COC pack be started.

For women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraceptive is recommended.

Several of the anti-HIV/HCV protease inhibitors (eg, ritonavir, telaprevir, boceprevir) and nonnucleoside reverse transcriptase inhibitors (eg, nevirapine) have been studied with coadministration of oral combination hormonal contraceptives; significant changes (increase or decrease) in the mean AUC of the estrogen or progestin have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitor for further drug-drug interaction information.

Strong and moderate CYP3A4 inhibitors such as azole antifungals (eg, ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (eg, clarithromycin, erythromycin), diltiazem and grapefruit juice, can increase plasma concentrations of the estrogen or the progestin or both. Increase in DRSP may increase serum potassium levels, possibly increasing the risk of hyperkalemia in high-risk patients (see **WARNINGS AND PRECAUTIONS, General**).

Oral contraceptives may also interfere with the metabolism of other drugs (see Table 5). Accordingly, plasma and tissue concentrations may either increase (eg, cyclosporine) or decrease (eg, lamotrigine).

Table 5 – Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.

Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another non-hormonal method of contraception.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another non-hormonal method of contraception.
	Lamotrigine	Decreased lamotrigine levels, may lead to breakthrough seizures	Use another non-hormonal method of contraception.
Antidiabetic drugs	Oral hypoglycemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another non-hormonal method of contraception. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen oral contraceptive or use another non-hormonal method of contraception.
	Beta blockers	Increased drug effect (decreased metabolism)	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic acid		Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors.	Avoid concomitant use.
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs	Adjust dose of drug as necessary, Discontinuing oral contraceptives can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine	Use with caution.
Cholesterol lowering agents	Clofibrate	Their action may be antagonized by oral contraceptives. Oral contraceptives may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Direct-acting antiviral (DAA) medicinal products	Ombitasvir, Paritaprevir,	Has been shown to be associated with increases in ALT levels 5 to > 20 times the upper limit of	See **CONTRAINDICATIONS**

	Ritonavir, with and without Dasabuvir	normal in healthy female subjects and HCV infected women	and **WARNINGS AND PRECAUTIONS,** Hepatic/Biliary/Pancreatic
Folic acid		Oral contraceptives have been reported to impair folate metabolism	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine	Use combination with caution
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs	Use other drugs or lower-dose oral contraceptives. If galactorrhea or hyperprolactinemia occurs, use other non-hormonal method of contraception.
Sedatives and hypnotics	Chlordiazepoxide Diazepam Lorazepam Oxazepam	Increased effect (increased metabolism)	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity	Use with caution, Monitor theophylline levels.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: eg, depression	Use with caution.
Vitamin B_{12}		Oral contraceptives have been reported to reduce serum levels of vitamin B_{12}	May need to increase dietary intake, or supplement.

In clinical studies, administration of a hormonal contraceptive containing ethinyl estradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (eg, midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (eg, theophylline) or moderately (eg, melatonin and tizanidine).

No formal drug-drug interaction studies have been conducted with ethinyl estradiol/ drospirenone.

Interactions with Drugs That Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Drospirenone and Ethinyl Estradiol Tablets USP with other drugs (see **WARNINGS AND PRECAUTIONS**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the drospirenone and ethinyl estradiol tablets clinical trials.

A drug-drug interaction study of DRSP 3 mg/estradiol 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/estradiol 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. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/estradiol 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 developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Herbal products containing St. John's wort (Hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Drug-Laboratory Test Interactions

Results of laboratory tests should be interpreted with the knowledge that the patient is taking an oral contraceptive. The following laboratory tests are modified:

A. Liver Function Tests
Aspartate serum transaminase (AST) - variously reported elevations
Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated

B. Coagulation Tests
Minimal elevation of test values reported for such parameters as prothrombin and factors VII, VIII, IX, and X.

C. Thyroid Function Tests
Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T_3 resin uptake.

D. Lipoproteins
Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.

E. Gonadotropins
LH and FSH levels are suppressed by the use of oral contraceptives. Wait 2 weeks after discontinuing the use of oral contraceptives before measurements are made.

F. Glucose Tolerance
Oral glucose tolerance remained unchanged or was slightly decreased.

Tissue Specimens
Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and PAP smears are submitted for examination.

Drug-Lifestyle Interactions

No studies on the effects of drospirenone and ethinyl estradiol on the ability to drive or use machines have been performed.

Metabolic Interactions

Drospirenone
Metabolism of drospirenone (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**: ***Metabolism***). 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 and CYP3A4 activity was investigated in clinical pharmacokinetic studies using omeprazole, simvastatin and midazolam as marker substrates. 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). Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. Based on the available results of in vivo and in vitro studies, it can be concluded that, at clinical dose level, DRSP shows little propensity to interact to a significant extent with cytochrome P450 enzymes.

Ethinyl estradiol
In vitro, ethinyl estradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2**.**

Noncontraceptive Benefits of Oral Contraceptives

Several health advantages other than contraception have been reported.

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.

2. Oral contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.

3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.

4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.

5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.

6. Oral contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.

7. Oral contraceptives have potential beneficial effects on endometriosis.

DOSAGE AND ADMINISTRATION

Tablets must be taken in the order directed on the package every day at about the same time. The patient may begin using Drospirenone and Ethinyl Estradiol Tablets USP on day 1 of her menstrual cycle (ie, the first day of menstrual flow), or on the first Sunday after her period begins. If the patient's period begins on Sunday, she should start that same day. If Drospirenone and Ethinyl Estradiol Tablets USP is taken later than day 1 when first starting medication, an additional (barrier) method of birth control is recommended for the first 7 days of use.

One hormone-containing brown to reddish brown tablet is to be taken daily for 24 consecutive days, followed by 1 hormone-free white to off-white tablet daily for 4 consecutive days. Withdrawal bleeding usually occurs within 2 to 3 days following administration of the last hormone-containing brown to reddish brown tablet (ie, while the patient is taking the hormone-free white to off-white tablets).

The patient begins each subsequent course of Drospirenone and Ethinyl Estradiol Tablets USP on the same day of the week that she began her first course. She begins taking her next course immediately after completion of the last course, regardless of whether or not withdrawal bleeding is still in progress.

Management of missed tablets: The patient should be instructed to use the following chart if she misses 1 or more of her birth control pills. She should be told to match the number of tablets missed with the appropriate starting time for her dosing regimen. The risk of pregnancy increases with each hormone-containing brown to reddish brown tablet missed.

Table 6 – Management of Missed Hormone-containing Brown to Reddish Brown Tablets

Sunday Start	Other Than Sunday Start
Miss One Brown to Reddish Brown Tablet at Any Time	**Miss One Brown to Reddish Brown Tablet At Any Time**
Take it as soon as you remember, and take the next tablet at the usual time. This means that you might take two tablets in one day	Take it as soon as you remember, and take the next tablet at the usual time. This means that you might take two tablets in one day.
Miss Two Brown to Reddish Brown Tablets in a Row	**Miss Two Brown to Reddish Brown Tablets in a Row**
First Two Weeks: 1. Take two tablets the day you remember and two tablets the next day. 2. Then take one tablet a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets	**First Two Weeks**: 1. Take two tablets the day you remember and two tablets the next day. 2. Then take one tablet a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets.
Third and Fourth Weeks 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month.	**Third and Fourth Weeks** 1. Safely dispose of the rest of the tablet pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 3. You may not have a period this month.

If you miss two periods in a row, call your doctor or clinic.	**If you miss two periods in a row, call your doctor or clinic.**
Miss Three or More Brown to Reddish Brown Tablets in a Row	**Miss Three or More Brown to Reddish Brown Tablets in a Row**
Anytime in the cycle. 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Anytime in the cycle.** 1. Safely dispose of the rest of the tablet pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

If the patient forgets any of the 4 hormone-free white to off-white tablets in week 4, she should be advised to safely dispose of the tablets she missed, and then to keep taking 1 tablet each day until the pack is empty. A back-up method of birth control is not required.

Special Notes on Administration

Switching from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch): The patient should start Drospirenone and Ethinyl Estradiol Tablets USP on the day she would normally start her next pack of combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using Drospirenone and Ethinyl Estradiol Tablets USP preferably on the day of removal, but at the latest when the next application would have been due.

Switching from a progestin-only method (mini-pill, injection) or from a Progestin-releasing Intrauterine System (IUS): The patient may switch from the mini-pill to Drospirenone and Ethinyl Estradiol Tablets USP on any day of her cycle. Patients using a progestin injection should start Drospirenone and Ethinyl Estradiol Tablets USP on the day the next injection is due. Patients using an IUS should start Drospirenone and Ethinyl Estradiol Tablets USP on the day the IUS is removed. In all cases, the patient should be advised to use an additional (barrier) method for the first 7 days of Drospirenone and Ethinyl Estradiol Tablets USP use.

Following first trimester abortion: The patient may start using Drospirenone and Ethinyl Estradiol Tablets USP immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second trimester abortion: Patients should be advised to start Drospirenone and Ethinyl Estradiol Tablets USP on day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the patient should be advised to use an additional (barrier) method for the first 7 days of Drospirenone and Ethinyl Estradiol Tablets USP use. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of use, or the woman should be advised to wait for her next menstrual period prior to starting Drospirenone and Ethinyl Estradiol Tablets USP. When the tablets are

administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered.

Withdrawal/breakthrough bleeding: Withdrawal bleeding usually occurs within 3 days following the last hormone-containing brown to reddish brown tablet. If spotting or breakthrough bleeding occurs while taking Drospirenone and Ethinyl Estradiol Tablets USP, the patient should be instructed to continue taking Drospirenone and Ethinyl Estradiol Tablets USP as prescribed and by the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult her physician.

Although the occurrence of pregnancy is unlikely if Drospirenone and Ethinyl Estradiol Tablets USP are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed dosing schedule (missed 1 or more hormone-containing tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

Advice in case of vomiting: If vomiting occurs within 3 to 4 hours after a tablet is taken, absorption may not be complete. In such an event, the advice concerning management of missed tablets is applicable.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

There have been no reports of overdose with Drospirenone and Ethinyl Estradiol Tablets USP. Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females. Withdrawal bleeding may even occur in girls before their menarche if they have accidentally taken the medicinal product. There are no antidotes and further treatment should be symptomatic, based on the knowledge of the pharmacological action of the constituents. Drospirenone is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium and evidence of metabolic acidosis should be monitored in cases of overdose. Liver function tests should be conducted, particularly transaminase levels, 2 to 3 weeks after consumption.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Drospirenone and Ethinyl Estradiol Tablets USP is a monophasic, combination oral contraceptive that contains the progestin drospirenone (3 mg) and a low dose of the estrogen ethinyl estradiol (0.02 mg) (41). Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes

in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. (42) Preclinical studies in animals and in vitro have shown that drospirenone has no androgenic, estrogenic, glucocorticoid and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity. (43, 44)

Estrogen-containing combinations such as Drospirenone and Ethinyl Estradiol Tablets USP increase the blood level of sex hormone binding globulin (SHBG), which is capable of binding and thus inactivating androgens such as testosterone. Moreover, the antiandrogenic activity of drospirenone partially counteracts the effects of endogenous androgens, blocking the binding of dihydrotestosterone (DHT) at the receptor level, which makes it a suitable option in the treatment of acne. Drospirenone may also help to reduce edema of the wall of the sebaceous follicle during the second half of the menstrual cycle, which is partly responsible for the flare-up of inflammatory lesions at this cycle phase.

Pharmacodynamics

Drospirenone inhibits ovulation and follicular development at an oral threshold dose of 2 mg. (45) Drospirenone 3 mg in combination with ethinyl estradiol was found to be optimal for inhibition of ovulation and cycle control. Administration of 3 extra days of hormone (drospirenone and ethinyl estradiol 24-day active versus a 21-day active of the same combined oral contraceptive) results in additional suppression of the ovary and of follicular development. This was observed in a study where hormone-containing pills of each regimen were intentionally missed on the first 3 days of the cycle and subsequent follicular development was monitored.

Drospirenone exhibited aldosterone antagonist activity at doses as low as 2 mg/day in healthy volunteers. Plasma renin activity and plasma aldosterone concentrations were increased, as was the excretion of aldosterone metabolites. The excretion of Na^+ was transiently increased by drospirenone (2 or 3 mg) alone or in combination with ethinyl estradiol. Serum Na^+ and K^+ concentrations remained unchanged. The potency of drospirenone was 6.6 times higher on average than that of spironolactone, using the Na^+/K^+ urinary ratio as the primary indicator of potency of the aldosterone antagonistic effect.

Drospirenone (2, 3, or 4 mg) in combination with ethinyl estradiol (0.02 mg) displayed a favourable effect on the lipid profile with an increase in HDL and a slight decrease in LDL. Total cholesterol remained unchanged. In addition, oral glucose tolerance was slightly increased, but remained within the reference range.

Drospirenone had no effect on the biosynthesis of sex hormone binding globulin (SHBG) and when administered in conjunction with ethinyl estradiol (0.02 mg), resulted in SHBG and corticosteroid binding globulin increases consistent with the dosage of ethinyl estradiol.

In vitro, drospirenone bound with low affinity to SHBG and did not bind at all to corticosteroid-binding globulin (CBG).

Pharmacokinetics

Table 7 – Summary of Pharmacokinetic Parameters[a] (Drospirenone 3 mg and Ethinyl Estradiol 0.02 mg) in Healthy Young Women

Cycle/Day	No. of subjects	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-24h)}$ (ng.h/mL)	$t_{1/2}$ (h)
Drospirenone					
1/1	23	38.4 (25.2%)	1.5 (1-2)	268 (18.9%)	nd
1/21	23	70.3 (14.5%)	1.5 (1-2)	763 (17.4%)	30.8 (21.9%)
Ethinyl Estradiol					
1/1	23	32.8 (44.9%)	1.5 (1-2.2)	108 (51.8%)	nd
1/21	23	45.1 (34.7%)	1.5 (1-2)	220 (57.4%)	nd

Abbreviations: AUC = area under the curve, C_{max} = maximum concentration, h = hour, mL = millilitre, nd = not determined, ng = nanogram, $t_{1/2}$ = elimination half life, t_{max} = time of maximum concentration

a The geometric mean is given for all parameters except t_{max}, with the geometric coefficient of variation in parentheses. For t_{max}, the median is given, with the range in parentheses.

Absorption

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. Serum concentrations of DRSP and EE reached peak levels within 1 to 2 hours after administration of drospirenone and ethinyl estradiol. After single-dose administration of drospirenone and ethinyl estradiol, the relative bioavailability, compared to a suspension was 107% and 97% for DRSP and EE, respectively.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of drospirenone and ethinyl estradiol, steady-state DRSP concentrations were observed after 8 days. There was about 2- to 3-fold accumulation in serum C_{max} and $AUC_{(0-24h)}$ values of DRSP following multiple-dose administration of drospirenone and ethinyl estradiol.

For EE, steady-state conditions are reported during the second half of a treatment cycle.
Following daily administration of drospirenone and ethinyl estradiol, serum C_{max} and $AUC_{(0-24h)}$ values of EE accumulate by a factor of about 1.5 to 2.0 (see Table 7 above).

Effect of Food

The rate of absorption of DRSP and EE following single administration of 2 tablets each containing 3 mg DRSP and 0.03 mg EE was slower under fed conditions, with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast the extent of absorption of EE was reduced by about 20% under fed conditions.

Distribution
DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4 to 5 L/kg.

DRSP does not bind to SHBG or CBG but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly, but nonspecifically, bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Metabolism
The 2 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 catalyzed by CYP3A4.

EE is subject to significant gut and hepatic first-pass metabolism. EE and its oxidative metabolites are primarily conjugated with glucuronides or sulfate. CYP3A4 in the liver are responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion
DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single- and multiple-dose regimens. Excretion of DRSP was nearly complete after 10 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 sulfate conjugates. In feces, about 17% to 20% of the metabolites were excreted as glucuronides and sulfates.

For EE, the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Special Populations and Conditions

Pediatrics
The safety and efficacy of drospirenone and ethinyl estradiol have not been established in women under the age of 14 years. Use of this product before menarche is not indicated.

Geriatrics
Drospirenone and Ethinyl Estradiol Tablets USP is not indicated for use in postmenopausal women.

Race
No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (aged 20-35 years) when drospirenone and ethinyl estradiol

were administered daily for 21 days. The effect of race on the disposition of drospirenone and ethinyl estradiol have not been evaluated.

Hepatic Insufficiency
Drospirenone and Ethinyl Estradiol Tablets USP is contraindicated in patients with hepatic dysfunction (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). The mean exposure to DRSP in women with moderate hepatic impairment is approximately 3 times higher than the exposure in women with normal hepatic function. The mean terminal half-life of DRSP for women with moderate hepatic impairment was 1.8 times greater than for women with normal hepatic function. Drospirenone and ethinyl estradiol tablets have not been studied in women with severe hepatic impairment.

Renal Insufficiency
Drospirenone and Ethinyl Estradiol Tablets USP is contraindicated in patients with renal insufficiency (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30-65) with normal renal function and mild and moderate 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, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those in the group with normal renal function (CLcr, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLcr, 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. Although hyperkalemia was not observed in the study, in 5 of the 7 subjects who continued use of potassium-sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range and who are concomitantly using potassium sparing drugs.

STORAGE AND STABILITY

Store in original packaging between 15°C and 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Drospirenone and Ethinyl Estradiol Tablets USP is available in a 28-day regimen.

Each blister pack contains 24 hormone-containing brown to reddish brown tablets and 4 hormone-free white to off-white tablets.

Description of the hormone-containing tablets: Brown to reddish brown, round, biconvex, film coated tablets debossed with ‘E3’ on one side

Description of the hormone-free tablets: White to off-white, round, biconvex, film coated tablets debossed with ‘E6’ on one side.

Each hormone-containing tablet contains 3 mg Drospirenone and 0.02 mg Ethinyl Estradiol.

Non-medicinal ingredients for the hormone-containing tablets: lactose monohydrate, corn starch, crospovidone, povidone, magnesium stearate, talc, hypromellose, titanium dioxide, and iron oxide red.

Non-Medicinal ingredients for the hormone-free tablets: lactose monohydrate, lactose anhydrous, microcrystalline cellulose, hypromellose, polacrilin potassium, magnesium stearate, titanium dioxide, polyethylene glycol and polysorbate.

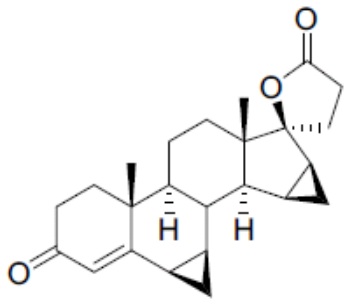
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Drospirenone:

Proper Name:	drospirenone
Chemical Name:	(2'*S*,6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*)-1,3',4',6,7,8,9,10,11,12,13,1 10,13-dimethylspiro[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*] phenanthrene-17,2'(5'*H*)-furan]-3,5'(2*H*)-dione
Structural Formula:	

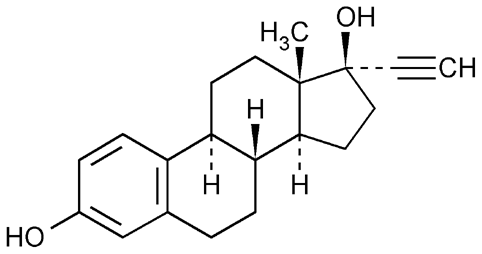


Drospirenone

Molecular Formula:	$C_{24}H_{30}O_3$
Molecular Weight:	366.50 g/mol
Description:	White to off-white powder. Freely soluble in methylene chloride; soluble in acetone and in methanol; sparingly soluble in ethyl acetate and in alcohol; practically insoluble in hexane and in water. Melting range is 198°C to 203°C.
pKa:	Neutral molecule without any acid-base properties in aqueous solutions (pH 1 to 12)
Partition coefficient:	log P_{OW} = 3.08

Ethinyl estradiol:

Proper Name:	ethinyl estradiol
Chemical Name:	19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol
Structural Formula:	



Molecular Formula:	$C_{20}H_{24}O_2$
Molecular Weight:	296.40 g/mol
Description:	White to practically white crystals or powder. Freely soluble in dioxane, diethyl ether, acetone, ethanol; soluble in chloroform; practically insoluble in water. Melting range is 180°C to 186°C.
pKa:	10.25 ± 0.04
Partition Coefficient:	log P_{OW} = 4.17 ± 0.03 (pH=5) 4.20 ± 0.04 (pH=7) 4.15 ± 0.04 (pH=9)

CLINICAL TRIALS

Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, comparative bioavailability study was conducted comparing Drospirenone and Ethinyl Estradiol Tablets USP (3 mg/0.02 mg × 2 tablets) of Glenmark Pharmaceuticals Canada Inc. and ^{Pr}YAZ® (drospirenone and ethinyl estradiol) tablets (3 mg/0.02 mg × 2 tablets) of Bayer Inc. Canada, in 38 healthy, adult, female, human subjects under fasting conditions.

Summary Tables of the Comparative Bioavailability Data

Drospirenone (2 x 3 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[@]	Reference[†]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{∞} (ng.hr/mL)	1926.68[*] 2027.95 (31.45)	1916.43[**] 1941.38 (25.79)	100.53	97.21 – 103.97
AUC_t (ng.hr/mL)	1749.46 1827.38 (29.23)	1746.24 1802.70 (25.60)	100.18	97.24 – 103.22
$AUC_{0\text{-}72h}$ (ng.hr/mL)	1253.15 1299.86 (26.89)	1249.63 1280.99 (22.15)	100.28	97.71 – 102.92
C_{max} (ng/mL)	88.47 92.18 (27.63)	93.63 97.17 (26.29)	94.49	87.97 – 101.48
T_{max}[#] (hr)	1.25 (0.50 - 4.00)	1.38 (0.75 - 4.00)		
$T_{½}$[$] (hr)	49.92 (22.68)[*]	49.30 (23.85)[**]		

[@] Drospirenone and Ethinyl Estradiol Tablets USP of Glenmark Pharmaceuticals Canada Inc.
[†] ^{Pr}YAZ® (3 mg drospirenone and 0.02 mg ethinyl estradiol) tablets of Bayer Inc., Canada.
*N = 37
**N = 35
[#] Expressed as the median (range) only.
[$] Expressed as the arithmetic mean (CV %) only.

Ethinyl estradiol (2 x 0.02 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[@]	Reference[†]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{∞} (pg.hr/mL)	1183.02 1229.34 (27.87)	1206.95 1264.08 (30.94)	98.02	95.20 – 100.92
AUC_t (pg.hr/mL)	1080.11 1125.20 (28.46)	1098.20 1152.11 (30.87)	98.35	95.34 – 101.46
C_{max} (pg/mL)	97.57 102.39 (30.76)	98.24 104.10 (33.38)	99.32	95.18 – 103.64
T_{max}[#] (hr)	1.50 (0.75 - 3.00)	1.50 (0.75 - 2.50)		
$T_{½}$[$] (hr)	19.81 (30.70)	19.99 (23.86)		

[@] Drospirenone and Ethinyl Estradiol Tablets USP of Glenmark Pharmaceuticals Canada Inc.
[†] [Pr]YAZ® (3 mg drospirenone and 0.02 mg ethinyl estradiol) tablets of Bayer Inc., Canada.
[#] Expressed as the median (range) only.
[$] Expressed as the arithmetic mean (CV %) only.

Contraception

General Information

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in 1 year.

Table 8: Reported Pregnancies per 100 Women per Year

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

Study Demographics and Trial Design

The contraceptive efficacy of drospirenone and ethinyl estradiol (0.02 mg ethinyl estradiol and 3 mg drospirenone/EE/DRSP) was evaluated in 2 pivotal phase III clinical trials. These studies (Studies 303740 and 308021) were large, open-label studies with the Pearl Index (PI) as primary criterion for the assessment of the contraceptive reliability.

Study 308020 was a comparison study with the following efficacy variables: cycle control, bleeding parameters, and the pregnancy rate expressed as PI.

An additional, single-center, controlled study (Study 301888) was conducted to investigate the impact of drospirenone and ethinyl estradiol on plasma lipids, hemostatic variables and carbohydrate metabolism. Bleeding patterns were also assessed.

Table 9: Overview of Studies Evaluating the Efficacy of Drospirenone and Ethinyl Estradiol for Conception Control

Study	Study Objective/ Design	Route of Administration/ Duration	Study Drug	No. of Subjects[a]	Mean Age (Range) [Years]	Mean BMI [kg/m^2]
303740 (46)	Pearl Index Multicenter, open, uncontrolled	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 13 cycles	Test product: Drospirenone and ethinyl estradiol (DRSP 3 mg + EE 0.02 mg) Placebo	1027	24.7 (18-35)	22.4±3.3
308021	Pearl Index Multicenter, open, uncontrolled	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 13 cycles	Test product: Drospirenone and ethinyl estradiol (DRSP 3 mg + EE 0.02 mg) Placebo	1101	24.7 (18-35)	21.7±2.8
308020	Bleeding pattern and cycle control Multicenter, open, randomized, parallel comparison	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 7 cycles One medicated tablet daily for 21 days followed by a 7-day tablet-free interval for 7 cycles	Test product: Drospirenone and ethinyl estradiol (DRSP 3 mg + EE 0.02 mg) Comparator[b]: DSG 0.150 mg + EE 0.02 mg	229 220	25.2 (18-35) 24.5 (18-35)	22.3±2.7 22.0±2.9
301888 (47)	Effect on lipid, hemostatic and carbohydrate profile Single center, open-label, randomized, controlled	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 7 cycles One medicated tablet daily for 21 days followed by a 7-day tablet-free interval for 7 cycles	Test product: Drospirenone and ethinyl estradiol (DRSP 3 mg + EE 0.02 mg)	29 30	23.8 (18-35) 23.7 (18-35)	21.8±2.9 21.7±1.8

			Comparator[b]: DSG 0.150 mg + EE 0.02 mg			

Abbreviations: BMI = Body Mass Index, DSG = desogestrel, DRSP = drospirenone, EE = ethinyl estradiol, kg = kilogram, m = meter, mg = milligram

a Full analysis set (FAS)

b Not available in Canada

Study Results

The total number of cycles under drospirenone and ethinyl estradiol treatment in the two 13-cycle pivotal oral contraception studies was 24,818 (11,421 in Study 303740 and 13,397 in Study 308021). For Pearl Index (PI) calculations, 13/28-day cycles constitute 1 woman-year (wy). The pooled PI was calculated to be 0.85 with an upper one-sided 97.5% confidence limit of 1.39, and this is equal to the upper limit of the corresponding two-sided 95% confidence interval (CI). The PI was calculated based on the 16 pregnancies observed during drospirenone and ethinyl estradiol treatment (Study 303740 with 11 pregnancies, PI=1.29 and Study 308021 with 5 pregnancies, PI=0.49) and a treatment exposure of 682,892 days (corresponding to 1,876.1 wy).

The adjusted Pearl Index (PI_c) in the drospirenone and ethinyl estradiol studies was calculated on the basis of 7 pregnancies rated as method failure (5 in Study 303740 and 2 in Study 308021) and a treatment exposure of 581,408 days (corresponding to 1,597.2 wy). The PI was calculated to be 0.44 with an upper 2-sided 95% confidence limit of 0.90 (see Table 10). The individual study PI_c and upper 2-sided 95% confidence limit values were 0.72 and 1.69 for Study 303740, and 0.22 and 0.80 for Study 308021, respectively.

Table 10: Pearl Index (PI) and Adjusted Pearl Index (PI_c) – Data of Studies 303740 and 308021

	Pooled		**Study 303740**		**Study 308021**	
	PI	**PI_c**	**PI**	**PI_c**	**PI**	**PI_c**
Total time of exposure (days/cycles/wy)	694,903/ 24,818/ 1,909		319,785/ 11,421/ 878.5		375,118/ 13,397/ 1,030.5	
Backup contraception (days)	12,011		7,842		4,169	
Noncompliant and/or backup contraceptive cycles (days)		113,495		67,504		45,991[a]
Relevant exposure time (days/cycles/wy)	682,892/ 24,389/ 1,876.1	581,408/ 20,765/ 1,597.2	311,943/ 11,141/ 856.9	252,281/ 9,010/ 693	370,949/ 13,248/ 1,019.1	329,127/ 11,755/ 904.2[b]
Number of pregnancies	16	7	11	5	5	2
PI and PI_c	**0.85**	**0.44**	**1.29**	**0.72**	**0.49**	**0.22**
Upper two-sided 95% confidence limit of PI and PI_c	1.39	0.90	2.30	1.69	1.14	0.80

Abbreviations: PI = Pearl Index; PI_c = adjusted Pearl Index; wy = woman-years

a For PI_c: days on back-up contraception and noncompliant days

b For PI_c: relevant treatment exposure time = time treatment exposure time minus days on cycles with back-up contraception and noncompliant days

In addition to the calculation of the PI, a life table analysis was performed for the time to the occurrence of a pregnancy in the two 13-cycle pivotal studies. The cumulative failure rate, ie, the

probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of unintended pregnancies considered to have occurred "during treatment."

The pooled Kaplan-Meier estimation after the last conception date after up to 1 year of treatment was 0.0085 with a 95% CI of 0.0052 to 0.0138, ie, the probability of contraceptive protection was estimated to be 0.9915 (99. 15%). The estimation of the 1-year pregnancy rate for Study 303740 was 1.26% with a 95% CI of 0.0052 to 0.0201, and for Study 308021 this was 0.5% with a 95% CI of 0.0021 to 0.0119.

Bleeding Pattern

A multicenter, randomized, open, parallel-group study (Study 308020) was conducted to evaluate the bleeding pattern, cycle control, and contraceptive reliability of 0.02 mg EE/3 mg DRSP (EE/DRSP) versus 0.02 mg EE/150 mg DSG (EE/DSG). Female subjects were randomized to EE/DRSP (n=230) or EE/DSG (n=223) for 7 cycles.

The bleeding pattern was also evaluated in a multicenter, uncontrolled study (Study 303740) in which women were treated with EE/DRSP (n=890) for 13 cycles.

The bleeding episodes were described using the Reference Period method recommended by the World Health Organization (WHO). The length of the Reference Period is 90 days**.**

A bleeding/spotting episode was defined as a number of days with bleeding/spotting preceded and followed by at least 2 bleeding-free days; correspondingly, a spotting-only episode was defined as a number of days with spotting preceded and followed by at least 2 bleeding-free days. A bleeding-free interval consisted of at least 2 days without bleeding/spotting preceded and followed by at least 1 day of bleeding/spotting. Bleeding pattern evaluations are presented for the FAS using means and standard deviations (SD).

An overview of the bleeding pattern parameters for both treatment groups in Study 308020 is presented in Table 11 for Reference Period 1 and Reference Period 2. The mean values for all the parameters studied were very similar in both treatment groups.

The results were similar for the per protocol set (PPS).

Table 11: Bleeding Pattern Parameters in Reference Period 1 and Reference Period 2 – FAS (Study 308020)

	n	Mean	SD
Reference Period 1			
Drospirenone and ethinyl estradiol			
Number of bleeding/spotting days	196	23.6	10.1
Number of bleeding/spotting episodes	196	4.4	1.0
Mean length of bleeding/spotting episodes (days)	196	5.6	3.3
Maximum length of bleeding/spotting episodes (days)	196	8.8	6.8
Number of spotting only days	196	9.5	7.1
Number of spotting only episodes	196	0.6	0.9
Mean length of spotting only episodes (days)	78[a]	2.6	1.6

Maximum length of spotting only episodes (days)	78[a]	3.0	2.4
Comparator[b]			
Number of bleeding/spotting days	165	24.0	8.5
Number of bleeding/spotting episodes	165	4.3	0.9
Mean length of bleeding/spotting episodes (days)	165	5.7	2.3
Maximum length of bleeding/spotting episodes (days)	165	8.6	5.5
Number of spotting only days	165	8.9	7.1
Number of spotting only episodes	165	0.5	0.8
Mean length of spotting only episodes (days)	54[a]	2.8	2.6
Maximum length of spotting only episodes (days)	54[a]	3.0	2.7
Reference Period 2			
Drospirenone and ethinyl estradiol			
Number of bleeding/spotting days	182	16.1	6.4
Number of bleeding/spotting episodes	182	3.4	1.1
Mean length of bleeding/spotting episodes (days)	180	4.8	1.5
Maximum length of bleeding/spotting episodes (days)	180	6.0	2.6
Number of spotting only days	182	6.2	4.8
Number of spotting only episodes	182	0.5	0.9
Mean length of spotting only episodes (days)	48[a]	3.0	2.2
Maximum length of spotting only episodes (days)	48[a]	3.6	2.8
Comparator[b]			
Number of bleeding/spotting days	153	16.6	8.5
Number of bleeding/spotting episodes	153	3.3	0.9
Mean length of bleeding/spotting episodes (days)	153	5.1	2.3
Maximum length of bleeding/spotting episodes (days)	153	6.3	5.5
Number of spotting only days	153	5.6	7.1
Number of spotting only episodes	153	0.3	0.8
Mean length of spotting only episodes (days)	32[a]	3.1	2.6
Maximum length of spotting only episodes (days)	32[a]	3.6	2.7

Abbreviations: FAS = full analysis set, n = number of subjects, SD = standard deviation

a n = number of volunteers with at least 1 spotting-only episode

b Not available in Canada

Bleeding pattern parameters for Study 303740 for Reference Periods 1 to 4 are presented in Table 12.

Table 12: Bleeding Pattern Parameters by Reference Period – Drospirenone and Ethinyl Estradiol Treatment Group - FAS (Study 303740)

	n	Mean	SD
Reference Period 1			
Number of bleeding/spotting days	890	22.49	10.34
Number of bleeding/spotting episodes	890	4.28	1.14
Mean length of bleeding/spotting episodes (days)	889	5.43	2.74
Max. length of bleeding/spotting episodes (days)	889	8.45	5.96
Number of spotting only days	890	7.72	7.67
Number of spotting only episodes	890	0.63	1.01
Mean length of spotting only episodes (days)	340	3.22	2.40
Maximum length of spotting only episodes (days)	340	3.80	3.02
Reference Period 2			
Number of bleeding/spotting days	853	15.09	7.36
Number of bleeding/spotting episodes	853	3.25	1.09

Mean length of bleeding/spotting episodes (days)	837	4.71	1.94
Max. length of bleeding/spotting episodes (days)	837	6.18	3.42
Number of spotting only days	853	5.16	5.31
Number of spotting only episodes	853	0.56	1.02
Mean length of spotting only episodes (days)	285	2.85	2.00
Maximum length of spotting only episodes (days)	287	3.20	2.25
Reference Period 3			
Number of bleeding/spotting days	792	14.48	6.98
Number of bleeding/spotting episodes	792	3.18	1.00
Mean length of bleeding/spotting episodes (days)	774	4.54	1.79
Max. length of bleeding/spotting episodes (days)	774	5.87	3.24
Number of spotting only days	792	5.04	5.64
Number of spotting only episodes	792	0.52	0.99
Mean length of spotting only episodes (days)	234	2.93	1.79
Maximum length of spotting only episodes (days)	236	3.42	2.45
Reference Period 4			
Number of bleeding/spotting days	719	14.56	7.23
Number of bleeding/spotting episodes	719	3.20	1.04
Mean length of bleeding/spotting episodes (days)	706	4.57	1.93
Max. length of bleeding/spotting episodes (days)	706	5.74	3.38
Number of spotting only days	719	5.16	5.82
Number of spotting only episodes	719	0.56	1.00
Mean length of spotting only episodes (days)	215	2.89	1.63
Maximum length of spotting only episodes (days)	234	3.25	2.23

Abbreviations: FAS = full analysis set, n = number of subjects, SD = standard deviation

The bleeding parameters (number of bleeding/spotting days, length of bleeding/spotting episodes and maximum length of bleeding/spotting episodes) decreased from Reference Period 1 to 2. After further treatment with drospirenone and ethinyl estradiol, in Reference Periods 3 and 4, these bleeding parameters remained relatively stable at around the level of Reference Period 2. A similar pattern was observed in the analysis of spotting-only days and episodes.

The results were similar for the PPS.

Cycle Control

A summary of withdrawal and intracyclic bleeding data is presented in Table 13 for the 3 pivotal studies, based on the FAS population.

Table 13: Frequency of Withdrawal and Intracyclic Bleeding – FAS

Cycle	Parameter No. of women with:	Study									
		303740		308020				301888			
		Drospirenone and ethinyl estradiol (EE/DRSP) n/N (%)		Drospirenone and ethinyl estradiol (EE/DRSP) n/N (%)		Comparator (EE/DSG)[a] n/N (%)		Drospirenone and ethinyl estradiol (EE/DRSP) n/N (%)		Comparator (EE/DSG)[a] n/N (%)	
1	WB	838/935	(89.6)	178/207	(86.0)	148/170	(87.1)	27/29	(93.1)	22/29	(75.9)
	IB	231/935	(24.7)	200/207	(96.6)	165/170	(97.1)	7/29	(24.1)	7/29	(24.1)
3	WB	821/874	(93.9)	187/196	(95.4)	156/166	(94.0)	26/27	(96.3)	27/28	(96.4)

	IB	121/874	(13.8)	34/196	(17.3)	27	(16.3)	7/27	(25.9)	4/28	(14.3)
6	WB	773/843	(91.7)	171/182	(94.0)	149/153	(97.4)	24/26	(92.3)	25/25	(100)
	IB	116/843	(13.8)	16/182	(8.8)	17/153	(11.1)	5/26	(19.2)	3/25	(12.0)
9	WB	709/763	(92.9)	-		-		-		-	
	IB	76/763	(10.0)	-		-		-		-	
13	WB	482/523	(92.2)	-		-		-		-	
	IB	81/523	(15.5)	-		-		-		-	

Abbreviations: DSG=desogestrel, DRSP=drospirenone, EE=ethinyl estradiol, FAS=full analysis set, IB=intracyclic bleeding; N=total number, n=number of subjects; WB=withdrawal bleeding

a Not available in Canada

Withdrawal Bleeding

Across all 3 studies, the majority of women had withdrawal bleeding. The percentage of volunteers with withdrawal bleeding was somewhat lower in cycle 1 (drospirenone and ethinyl estradiol: 86.0% to 93.1% vs comparator: 75.9% to 87.1%) than in subsequent cycles, when at least 91.7% of subjects treated with drospirenone and ethinyl estradiol and 92.3% of women in the comparator group experienced withdrawal bleeding.

The mean length of withdrawal bleeding decreased for both treatment groups from cycle 1 (drospirenone and ethinyl estradiol: 5.2 to 7.3 days; comparator: 5.4 to 6.7 days) to cycle 6 (drospirenone and ethinyl estradiol: 4.7 to 4.8 days; comparator: 5.2 to 5.3 days) with a slightly more pronounced decrease in the drospirenone and ethinyl estradiol group. In the drospirenone and ethinyl estradiol group, the mean length of withdrawal bleeding remained similar in cycle 9 (4.8 days), but further decreased to 2.6 days in cycle 13.

Intracyclic Bleeding

About one-quarter of the women in both the drospirenone and ethinyl estradiol and comparator treatment groups of Studies 303740 and 301888 experienced intracyclic bleeding during cycle 1. In Study 308020, the withdrawal bleeding at study entry, on the first day of which the subjects had to take the first dose of study medication, was counted as intracyclic bleeding. Therefore, in this study the majority of women in both treatment groups had intermenstrual bleeding reported for cycle 1 (drospirenone and ethinyl estradiol: 96.6%; comparator: 97.1%). However, across all studies and in both treatment groups the proportion of volunteers with intracyclic bleeding decreased to below one-fifth by cycle 6 (drospirenone and ethinyl estradiol: 8.8% to 19.2%; comparator: 11.1% to 12.0%). With continued treatment, in the drospirenone and ethinyl estradiol group the number of subjects who had intracyclic bleeding remained in the same range (cycle 9: 10.0%; cycle 13: 15.5%).

The mean length of intracyclic bleeding was similar between treatment groups and in general decreased from cycle 1 (drospirenone and ethinyl estradiol: 4.7 to 8.4 days; comparator: 8.1 to 10.6 days) to cycle 6 (drospirenone and ethinyl estradiol: 0.3 to 4.5 days; comparator: 0.5 to 5 days). In 1 study with longer drospirenone and ethinyl estradiol treatment, the mean duration of intracyclic bleeding remained stable up to cycle 13 (4.5 to 4.8 days).

The mean number of intracyclic bleeding episodes per cycle was very low and varied between 0.1 and 1.4 for the drospirenone and ethinyl estradiol-treated subjects and between 0.1 and 1.3 for the women in the comparator treatment group throughout the treatment period.

While more than one-half of women in both treatment groups experienced intracyclic bleeding of normal intensity in cycle 1, the predominant mean maximum intensity of intracyclic bleeding from cycle 2 onwards was spotting in both treatment groups. Intracyclic bleeding of normal and light intensity was equally distributed in most treatment cycles for both groups. Intracyclic bleeding of heavy intensity was only recorded for a few women.

From cycle 1 onwards, a decrease in the mean maximum length of intracyclic bleeding episodes was noted for drospirenone and ethinyl estradiol and comparator-treated women. The mean maximum length of intracyclic bleeding episodes ranged from approximately 5 to 6 days from cycles 2 to 12 in the drospirenone and ethinyl estradiol group and from 5 to 7 days in the comparator group from cycles 2 to 6.

The results were similar for the PPS

Acne Therapy

Study Demographics and Trial Design

The efficacy of drospirenone and ethinyl estradiol in treating moderate acne vulgaris was evaluated in 2 pivotal, multicentre, double-blind, randomized clinical trials carried out in North America. An overview of the 2 studies is presented below in Table 14:

Table 14: Overview of Studies Evaluating the Efficacy of Drospirenone and Ethinyl Estradiol in the Treatment of Moderate Acne Vulgaris

Study	Study Objective/ Design	Route of Administration/ Duration	Study Drug	No. of Subjects[a]	Mean Age (Range) [Years][b]	Mean BMI [kg/m^2][b]
306820	Efficacy/Safety Multicentre, double-blind, randomized	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 6 cycles	Test product: Drospirenone and ethinyl estradiol (DRSP 3 mg + EE 0.02 mg)	229	25.2 (14-44)	24.0 ± 4.0
			Placebo	227	25.4 (14-45)	25.1 ± 4.9
306996	Efficacy/Safety Multi-centre, double-blind, randomized	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 6 cycles	Test product: Drospirenone and ethinyl estradiol (DRSP 3 mg + EE 0.02 mg)	222	25.2 (14-44)	23.8 ± 4.6
			Placebo	215	25.1 (14-44)	23.8 ± 4.4

Abbreviations: BMI = Body Mass Index, DRSP = drospirenone, EE = ethinyl estradiol, kg = kilogram, m = meter, mg = milligram

a Amended full analysis set (Amended FAS)

b Full analysis set (FAS)

In the early course of the studies, the original diagnosis, "mild to moderate acne vulgaris", was amended to "moderate acne vulgaris." The amended FAS was considered the primary efficacy analysis. Table 15 provides an overview of the primary efficacy variable results based on the amended FAS. Drospirenone and ethinyl estradiol produced clinically and statistically significant anti-acne effects in all primary efficacy variables. These results are presented in detail below.

The primary efficacy variables were the percentage change from baseline to endpoint (ie, cycle 6 data with missing values replaced in accordance with the last observation carried forward [LOCF] procedure) in inflammatory lesion counts (including papules, pustules, and nodules), noninflammatory lesion counts (including open and closed comedones), and total lesion counts, as well as the percentage of women classified as "0" (clear skin) or "1" (almost clear skin) on the 6-point Investigator Static Global Assessment (ISGA) scale.

Study Results

Study 306820

Female subjects were randomized to drospirenone and ethinyl estradiol (n=266) or placebo (n=268) for 6 treatment cycles. The reduction from baseline to endpoint in mean percentage inflammatory lesion count was 47.8% for drospirenone and ethinyl estradiol versus 32.7% for placebo. The adjusted mean difference was –14.932% (P <0.0001 for drospirenone and ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage noninflammatory lesion count was 38.4% for drospirenone and ethinyl estradiol versus 18.2% for placebo. The adjusted mean difference was –20.085% (P <0.0001 for drospirenone and ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage total lesion count was 42.6% for drospirenone and ethinyl estradiol versus 25.4% for placebo. The adjusted mean difference was –17.063% (P <0.0001 for drospirenone and ethinyl estradiol versus placebo). The reductions in inflammatory lesion count, noninflammatory lesion count, and total lesion count over time (from baseline to each visit) were statistically significant within both the drospirenone and ethinyl estradiol and placebo groups.

For the investigator's global assessment, improvement of facial acne (eg, subjects rated as "clear" or "almost clear") was observed in subjects treated with drospirenone and ethinyl estradiol (16.2%) and placebo (4.4%). The resulting odds ratio was 4.447 (confidence interval [CI]: 2.184, 9.880; P <0.0001).

The results for the PPS and FAS were consistent with those for the amended FAS.

Study 306996

A total of 538 women (270 in the drospirenone and ethinyl estradiol group and 268 in the placebo group) were randomized and dispensed study medication. After 6 treatment cycles, the reduction from baseline to endpoint in mean percentage inflammatory lesion count was 50.9% for drospirenone and ethinyl estradiol versus 34.7% for placebo. The adjusted mean difference was –15.752% (P <0.0001 for drospirenone and ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage noninflammatory lesion count was 42.8% for drospirenone and ethinyl estradiol versus 26.3% for placebo. The adjusted mean difference was -

16.010% (*P* <0.0001 for drospirenone and ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage total lesion count was 46.5% for drospirenone and ethinyl estradiol versus 30.9% for placebo. The adjusted mean difference was –15.194% (*P* <0.0001 for drospirenone and ethinyl estradiol versus placebo). The reductions in inflammatory lesion count, noninflammatory lesion count, and total lesion count over time (from baseline to each visit) were statistically significant within both the drospirenone and ethinyl estradiol and placebo groups.

For the investigator's global assessment, improvement of facial acne (eg, subjects rated as "clear" or "almost clear") was observed in subjects treated with drospirenone and ethinyl estradiol (21.2%) and placebo (9.3%). The resulting odds ratio was 2.921 (CI: 1.598, 5.341; *P* =0.0004).

The results for the PPS and FAS were consistent with those for the amended FAS.

Table 15: Overview of Primary Efficacy Variable Results - Amended FAS (Pooled Data of Studies 306820 and 306996)

Amended FAS Drospirenone and ethinyl estradiol: N= 451 Placebo: N=442	Percent Change from Baseline to Endpoint			ISGA
	Inflammatory Lesions	Noninflammatory Lesions	Total Lesions	
	Drospirenone and ethinyl estradiol: n=450 Placebo: n=442	Drospirenone and ethinyl estradiol: n=450 Placebo: n=442	Drospirenone and ethinyl estradiol: n=450 Placebo: n=442	Drospirenone and ethinyl estradiol: n=451 Placebo: n=442
Drospirenone and ethinyl estradiol versus Placebo[a]	-15.348%	-18.091%	-16.148%	3.413[b]
95% CI	-20.427%, -10.268%	-23.553%, -12.629%	-20.685%, -11.612%	2.146, 5.426
P value	*P* <0.0001	*P* <0.0001	*P* <0.0001	*P* <0.0001

Abbreviations: CI = confidence interval, FAS = full analysis set, ISGA = Investigator Static Global Assessment, N = total number, n = number of subjects

a Difference in adjusted treatment means (ie, drospirenone and ethinyl estradiol minus placebo)

b *P* value, odds ratio, and confidence limits computed from Cochran Mantel-Haenszel statistic stratified by pooled center, since the logistic regression model did not converge.

DETAILED PHARMACOLOGY

Animal Pharmacology

Drospirenone

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 mcg/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 mcg/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 (0.3-10 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 5 to 10 times more potent than spironolactone, and its aldosterone antagonist activity was not affected by concomitant administration of ethinyl estradiol. (48) 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.

Drospirenone in subcutaneous doses of 1 or 10 mg/animal/day did not prevent hormone deficiency-induced trabecular bone loss in ovariectomized rats after treatment for 24 weeks. In addition, drospirenone in both tested doses did neither impair nor enhance the bone protective effect of ethinyl estradiol on trabecular bone after 24 weeks of treatment.

When drospirenone (30 mg/kg/day) was subcutaneously administered to ovariectomized telemetered normotensive rats, only a slight increase in heart rate was found. However, this finding was not accompanied by any changes in systolic or diastolic blood pressure. The effects produced by 0.01 mg/kg/day ethinyl estradiol (increased systolic blood pressure and lowered heart rate) were reduced when ethinyl estradiol was coadministered with drospirenone. Drospirenone in subcutaneous doses of 1 or 10 mg/animal/day had no effect on liver-derived parameters (serum angiotensinogen and IGF-I) in ovariectomized rats after 11 treatment days.

In safety pharmacology studies, oral administration of drospirenone or drospirenone in combination with ethinyl estradiol had no effect on pentylenetetrazole- or maximal electroshock-induced seizure activity in mice. When drospirenone was administered to rats as a single oral dose in combination with ethinyl estradiol (100:1), a dose-dependent increase in urine volume and Na^+ excretion, coupled with a dose-dependent decrease in urinary creatinine clearance, K^+ and Cl^- excretion and BUN was observed. These effects on renal function were attributed to the antimineralocorticoid activity of drospirenone.

Ethinyl Estradiol

Ethinyl estradiol is a potent estrogen with qualities similar to estradiol. In contrast to estradiol, it is highly effective after oral administration. The relative oral potency of ethinyl estradiol's antigonadotropic and antifertility effects (eg, inhibition of ovulation, inhibition of implantation) is 3 to 30 times higher than that of orally administered estradiol.

Ethinyl estradiol also exhibits effects on carbohydrate, protein, and lipid metabolism similar to those of other estrogens: in rats, hepatic glycogen content and serum triglycerides are significantly increased, whereas serum cholesterol is decreased. In addition, a small but significant increase in the liver weight can be seen. Phospholipids were also raised after treatment for 1 month. The effects on lipid and carbohydrate metabolism may be attributed to an indirect glucocorticoid activity of estrogens. It is well established that estrogens in the rat cause a stimulation of the adrenals and a depletion of corticoids. The increased glucocorticoid level may be responsible for an induction of gluconeogenesis concomitant with high fasting blood glucose levels.

Following administration of ethinyl estradiol alone in ovariectomized rats, observations included dose-dependently higher uterine weights. Partial reversal of the stimulatory effect of ethinyl estradiol on uterine weight was observed following administration of drospirenone (10 mg/animal/day) in combination with ethinyl estradiol (0.0001, 0.001 mg/animal/day).

TOXICOLOGY

Acute Toxicity

Drospirenone

Table 16 below summarizes the median lethal doses (LD_{50}) determined in acute toxicity studies with drospirenone.

Table 16 – LD_{50} 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, including 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, was investigated after daily intragastric administration of the following doses.

Table 17 – Long-term Toxicity Studies Conducted With Drospirenone (DRSP) and Ethinyl Estradiol (EE)

Species	No./Group	Dose (mg/kg/day)			Treatment Period
		DRSP+EE	DRSP Alone	EE Alone	
Mouse	25-30F	0+0, 3+0.03, 10+0.1, 30+0.3	3, 10, 30	0.03, 0.1, 0.3	14-15 weeks
Rat	6F	--	0, 10, 50, 100	--	7 days
Rat	20F	0+0, 1+0.01, 3+0.03, 10+0.1	1, 3, 10	0.01, 0.03, 0.1	14 weeks
Rat	25F	--	0, 0.6, 3, 15	--	27 weeks
Rat	20F	0+0, 0.3+0.003, 3+0.03, 10+0.1	--	--	52-53 weeks
Monkey	4F	--	0, 0.2, 2, 10	--	27 weeks
Monkey	4-5F	0+0, 0.3+0.03, 3+0.3, 10+1	3, 1.0	0.03, 0.1	53-54 weeks

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 $AUC_{(0\text{-}24h)}$ 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 of the following doses.

Table 18 – Carcinogenicity Studies Conducted with Drospirenone (DRSP) and Ethinyl Estradiol (EE)

Species	No./Group	Dose (mg/kg/day)			Treatment period
		DRSP +EE	DRSP Alone	EE Alone	
Mouse	55F or 110F	0+0, 1+0.01, 3+0.03, 10+0.1	1, 3,10	0.01, 0.03, 0.1	104 weeks
Rat	55F or 110F	0+0, 0.3+0.003, 3+0.03, 10+1	0.3, 3, 10	0.003, 0.03, 1	106-110 weeks

No carcinogenicity was observed after two 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 on the liver 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 $AUC_{(0\text{-}24h)}$ 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 1000 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 mcg/mL. Intragastric administration of drospirenone 10 mg/kg/day to rats for 14 consecutive days generated two forms of DNA adducts in male and female rat livers. Low levels of 3 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 mcg/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.

Drospirenone did not demonstrate clastogenic potential in human lymphocytes in vitro at concentrations that were cytotoxic or precipitating in the presence or absence of extrinsic metabolic activation. No DNA adducts were detected in primary hepatocytes isolated from female rats incubated with 3.62 mcM tritiated-drospirenone in vitro.

Based on the highest dose given in the mouse micronucleus study, the specification level of 0.1% and the expected maximum human intake of the impurity contained in a daily (3 mg) dose of drospirenone, the results of the mouse micronucleus test support a safety margin of 5×10^5.

Following oral administration of drospirenone to juvenile rats for 5 days in a dose range-finding study, serum liver enzymes (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) were not altered at doses up to 500 mg/kg/day. Therefore, the high dose of 500 mg/kg/day was considered an adequate, nonhepatotoxic dose for a rat liver foci bioassay (which was subsequently cancelled for drospirenone when long-term data became available for drospirenone).

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 at the following doses:

Table 19 – Reproductive Toxicity Studies Conducted With Drospirenone (DRSP) + Ethinyl Estradiol (EE)

Segment	Species	No./Group	Dose (mg/kg/day) DRSP+ EE	Treatment Period
I: Fertility and General Reproductive Performance	Rat	25F	0+0; 5+0.05; 15+0.15; 45+0.45	42 Days prior to mating.
	Rat	25F	0+0; 1+ 0.01; 3+0.03; 10+0.1	Days 0 to 6 of gestation.
II: Embryotoxicity/ Teratogenicity	Rat	36F	0+0; 5+0; 15+0; 45+0	Days 6 to 15 of gestation.
	Rat	16F	0+0; 5+0.05; 15+0.15; 45+0.45	Days 14 to 21 of gestation
	Rabbit	20F	0+0; 10+0; 30+0; 100+0	Days 6 to 18 of gestation
	Rabbit	164F-182F	0+0; 30+0	Days 6 to 18 of gestation
	Monkey	12F	0+0;1+0.01; 3+0.03; 10+0.1	Days 20 to 90 of gestation
III: Perinatal/Postnatal Toxicity	Rat	10F	15+0.15; 45+0.45	Day 15 of gestation to day 3 postpartum
	Rat	35F	0+0; 5+0.05; 15+0.15; 45+0.45	Days 15 to 18 of gestation and days 1 to 22 postpartum

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 the drug product.

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.

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PART III: CONSUMER INFORMATION

[Pr]Drospirenone and Ethinyl Estradiol Tablets USP
Drospirenone and Ethinyl Estradiol Tablets

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

ABOUT THIS MEDICATION

What the medication is used for:

- To prevent pregnancy
- To treat moderate acne vulgaris in women 14 years of age and older who are able to use birth control pills and have achieved menarche. Your first menstrual period is referred to as menarche.

What it does:

Drospirenone and Ethinyl Estradiol Tablets USP is a birth control pill (oral contraceptive) that contains two female sex hormones, the progestin drospirenone (3 mg) and a low dose of the estrogen ethinyl estradiol (0.02 mg). Both hormones are synthetic and similar to those that occur naturally in your body. The Drospirenone and Ethinyl Estradiol Tablets USP pill pack has 24 hormone-containing brown to reddish brown "active" pills to be taken for 24 days, followed by 4 hormone-free white to off-white "reminder" pills to be taken for four days. It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.

Birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).

Drospirenone in Drospirenone and Ethinyl Estradiol Tablets USP helps with androgen- (male sex hormone) related skin problems. Androgen circulates naturally within the female body. Androgens can cause glands in the skin to over-produce oil. This results in acne. Drospirenone and Ethinyl Estradiol Tablets USP works by lowering androgen levels in the body and by blocking the effects of androgens at the gland. As a result, a reduction in the number of acne breakouts is associated with Drospirenone and Ethinyl Estradiol Tablets USP treatment.

Effectiveness of Birth Control Pills

Combination birth control pills are more than 99 percent effective in preventing pregnancy when:

- the pill is **TAKEN AS DIRECTED**, and
- the amount of estrogen is 20 micrograms or more.

A 99 percent effectiveness rate means that if 100 women used birth control pills for one year, one woman in the group would get pregnant.

The chance of becoming pregnant increases with incorrect use.

Other Ways to Prevent Pregnancy

Other methods of birth control are available to you. They are usually less effective than birth control pills. When used properly, however, other methods of birth control are effective enough for many women.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year:

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

Pregnancy rates vary widely because people differ in how carefully and regularly they use each method. (This does not apply to IUDs since they are implanted in the uterus.). Regular users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

The effective use of birth control methods other than birth control pills and IUDs requires more effort than

taking a single pill every day. It is an effort that many couples undertake successfully.

When it should not be used:

The birth control pill is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. The use of the birth control pill always should be supervised by your doctor.

You should not use Drospirenone and Ethinyl Estradiol Tablets USP if you have or have had any of the following conditions:

- blood clots in the legs, lungs, eyes, or elsewhere, or thrombophlebitis (inflammation or swelling of the veins)
- stroke, heart attack, or coronary artery disease (eg, angina pectoris), or a condition that may be a first sign of a stroke (such as a transient ischemic attack or small reversible stroke)
- disease of the heart valves with complications
- known abnormalities of the blood clotting system that increases your risk for developing blood clots
- severe high blood pressure
- diabetes with complications
- very high blood cholesterol or triglyceride levels
- you smoke and are over age 35
- migraine headache
- you are scheduled for major surgery
- prolonged bed rest
- you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C
- jaundice (yellowing of the eyes or skin), liver disease or liver tumor
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependent cancer
- unusual vaginal bleeding without a known reason
- loss of vision due to blood vessel disease of the eye
- you are pregnant or suspect you may be pregnant
- pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood
- allergy (hypersensitivity) to ethinyl estradiol, drospirenone, or to any of the other ingredients in Drospirenone and Ethinyl Estradiol Tablets USP (see **What the medicinal ingredients are** and **What the nonmedicinal ingredients are**)

In addition, you should not use Drospirenone and Ethinyl Estradiol Tablets USP if you have any of the following conditions:

- Kidney disease
- Liver disease
- Adrenal disease

Tell your doctor if you have ever had any of the above conditions (your doctor can recommend another method of birth control).

What the medicinal ingredients are:

drospirenone and ethinyl estradiol

What the nonmedicinal ingredients are:

Non-medicinal ingredients for the hormone-containing tablets: lactose monohydrate, corn starch, crospovidone, povidone, magnesium stearate, talc, hypromellose, titanium dioxide, and iron oxide red.

Non-medicinal ingredients for the hormone-free tablets: lactose monohydrate, lactose anhydrous, microcrystalline cellulose, hypromellose, polacrilin potassium, magnesium stearate, titanium dioxide, polyethylene glycol and polysorbate.

What dosage forms it comes in:

Drospirenone and Ethinyl Estradiol Tablets USP is available in a 28-day regimen.

Each blister pack contains 24 hormone-containing brown to reddish brown tablets and 4 hormone-free white to off-white tablets.

Description of the hormone-containing tablets: Brown to reddish brown, round, biconvex, film coated tablets debossed with ‘E3’ on one side

Description of the hormone-free tablets: White to off-white, round, biconvex, film coated tablets debossed with ‘E6’ on one side.

Each hormone-containing tablet contains 3 mg Drospirenone and 0.02 mg Ethinyl Estradiol.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including Drospirenone and Ethinyl Estradiol Tablets USP, should not be used by women who are over 35 years of age and smoke. Women should not smoke.

Birth control pills DO NOT PROTECT against sexually transmitted infections (STIs), including HIV/AIDS.

For protection against STIs, it is advisable to use latex or polyurethane condoms IN COMBINATION WITH birth control pills.

Drospirenone and Ethinyl Estradiol Tablets USP is a birth control pill containing estrogen and progestin. The progestin in Drospirenone and Ethinyl Estradiol Tablets USP is known as drospirenone and it may increase the levels of potassium in your blood. Therefore, you should not take Drospirenone and Ethinyl Estradiol Tablets USP if you have kidney, liver, or adrenal disease (a disease that may alter the body's fluid and mineral balance) because this could cause serious heart and health problems. Other drugs may also increase potassium (see Before you use Drospirenone and Ethinyl Estradiol Tablets USP, talk to your doctor or pharmacist if you). During the first month that you take Drospirenone and Ethinyl Estradiol Tablets USP, you should have a blood test to check your potassium level.

Do not use Drospirenone and Ethinyl Estradiol Tablets USP if you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C. Using these drugs at the same time as Drospirenone and Ethinyl Estradiol Tablets USP has the potential to cause liver problems, such as an increase in the ALT liver enzyme. You can usually start Drospirenone and Ethinyl Estradiol Tablets USP about 2 weeks after finishing treatment with this combination of drugs used for Hepatitis C, but always consult with your doctor or pharmacist.

It has been reported that drospirenone, the progestin in Drospirenone and Ethinyl Estradiol Tablets USP, may carry a higher risk of blood clots than some other progestins (including levonorgestrel). You should talk to your doctor about the available options.

BEFORE you use Drospirenone and Ethinyl Estradiol Tablets USP, talk to your doctor or pharmacist if you:

- smoke
- are overweight
- have a history of breast disease (eg, breast lumps) or a family history of breast cancer
- have high blood pressure
- have high cholesterol
- have diabetes
- have heart or kidney disease
- have a history of seizures/epilepsy
- have a history of depression
- have a history of liver disease or jaundice
- wear contact lenses
- have uterine fibroids (benign tumors of the uterus)
- may be pregnant or are breast feeding
- have systemic lupus erythematosus
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have haemolytic uremic syndrome
- have sickle cell disease
- have any problems with the valves in your heart and/or have an irregular heart rhythm
- 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, or airway passages
- **you 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 treatment of arthritis or other problems (eg, ibuprofen, naproxen or others)**
  - **Potassium-sparing diuretics (spironolactone and others)**
  - **Potassium supplements**
  - **ACE inhibitors and Angiotensin-II receptor antagonists for the treatment of high blood pressure (eg, captopril, enalapril, lisinopril, losartan, valsartan, irbesartan, or others)**
  - **Heparin**

You should also inform your doctor about a family history of blood clots, heart attacks, or strokes.

If you see a different doctor, inform him or her that you are using Drospirenone and Ethinyl Estradiol Tablets USP.

Tell your doctor if you are scheduled for any laboratory tests since certain blood tests may be affected by hormonal contraceptives.

Also tell your doctor if you are scheduled for **MAJOR** surgery. You should consult your doctor about stopping the use of Drospirenone and Ethinyl Estradiol Tablets USP four weeks before surgery and not using Drospirenone and Ethinyl Estradiol Tablets USP for a time period after surgery or during bed rest.

Drospirenone and Ethinyl Estradiol Tablets USP should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year. Use Drospirenone and Ethinyl Estradiol Tablets USP only on the advice of your doctor and carefully follow all directions given to you. You must use the birth control pill exactly as prescribed. Otherwise, you may become pregnant.

If you and your doctor decide that, for you, the benefits of Drospirenone and Ethinyl Estradiol Tablets USP outweigh the risks, you should be aware of the following:

THE RISKS OF USING DROSPIRENONE AND ETHINYL ESTRADIOL TABLETS USP

1. Circulatory disorders (including blood clot in legs, lungs, heart, eyes, or brain)

Women who use hormonal contraceptives have a higher incidence of blood clots. Blood clots are the most common serious side effects of birth control pills. The risk of developing blood clots is especially high during the first year a woman ever uses a hormonal contraceptive or restarts the same or a different hormonal contraceptive. Clots can occur in many parts of the body.

Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

- sharp pain in the chest which may increase with deep breathing; coughing blood; sudden shortness of breath or rapid breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg; red or discoloured skin on the leg. These symptoms could indicate a possible blood clot in the leg.
- crushing chest pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats. These symptoms could indicate a possible heart attack.
- sudden severe or worsening headache or vomiting; sudden trouble walking, dizziness, loss of balance or coordination; loss of consciousness or fainting with or without seizure; sudden confusion, disturbances of vision, speech or understanding; sudden weakness or numbness of the face, arm or leg. These symptoms could indicate a possible stroke.
- sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.
- other signs of a blood clot can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision or in a blood vessel leading to an arm or leg, resulting in damage to or loss of a limb.

The risk of clotting seems to increase with higher estrogen doses. It is important, therefore, to use as low a dosage of estrogen as possible.

Cancer of the breast, cervix, or liver may be life-threatening or may result in death.

2. Breast cancer

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

Some women who use hormonal contraceptives may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term users of birth control pills (more than

eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small, however. A yearly breast examination by a health care professional is recommended for all women.

ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.

3. Cervical cancer

Some studies have found an increase of cancer of the cervix in women who use hormonal contraceptives, although this finding may be related to factors other than the use of oral contraceptives. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

4. Liver tumors

The short and long-term use of birth control pills have also been linked with the growth of liver tumors. Such tumors are **extremely** rare.

Contact your doctor immediately if you experience severe pain or a lump in the abdomen.

5. Gallbladder disease

Users of birth control pills have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

6. Use in pregnancy

Birth control pills should not be taken by pregnant women. There is no evidence, however, that the birth control pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

7. Use after pregnancy, miscarriage, or an abortion

Your doctor will advise you of the appropriate time to start the use of Drospirenone and Ethinyl Estradiol Tablets USP after childbirth, miscarriage, or therapeutic abortion.

8. Pregnancy after stopping Drospirenone and Ethinyl Estradiol Tablets USP

You will have a menstrual period when you stop using Drospirenone and Ethinyl Estradiol Tablets USP. You should delay pregnancy until another menstrual period occurs within four to six weeks. In this way the pregnancy can be more accurately dated. Contact your doctor for recommendations on alternate methods of contraception during this time.

9. Use while breastfeeding

If you are breastfeeding, consult your doctor before starting the birth control pill. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. Adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of contraception and only consider starting the birth control pill once you have weaned your child completely.

INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also tell any other doctor or dentist (or the dispensing pharmacist) who prescribes another drug that you use Drospirenone and Ethinyl Estradiol Tablets USP. They can tell you if you need to use an additional method of contraception and if so, for how long.

Drugs that may interact with Drospirenone and Ethinyl Estradiol Tablets USP include:

- drugs used for the treatment of epilepsy (eg, primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate); tuberculosis (eg, rifampin, rifabutin), HIV infections (eg, ritonavir, nevirapine) and Hepatitis C Virus infections (eg boceprevir, telaprevir)
- antibiotics (eg, penicillins, tetracyclines, clarithromycin, erythromycin) for infectious diseases
- cyclosporine
- ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (used to treat Hepatitis C)
- antifungals (eg, griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole)
- cholesterol-lowering drugs (eg, clofibrate)

- drugs used for the treatment of certain heart diseases or high blood pressure (eg, diltiazem, verapamil)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (eg, benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (meperidine)
- antidepressants (eg, clomipramine)
- tizanidine (drug used for multiple sclerosis [MS])
- theophylline (drug used for asthma)
- some nutritional supplements (eg, Vit. B12, folic acid)
- antacids (use 2 hours before or after taking Drospirenone and Ethinyl Estradiol Tablets USP)

Drospirenone and Ethinyl Estradiol Tablets USP may also interfere with the working of other drugs.

Herbal or food products that may interfere with Drospirenone and Ethinyl Estradiol Tablets USP include:

- the herbal remedy St. John's wort (primarily used for the treatment of depressive moods)
- grapefruit juice

This is not a complete list of possible drug interactions with Drospirenone and Ethinyl Estradiol Tablets USP. Talk to your doctor for more information about drug interactions.

PROPER USE OF THIS MEDICATION

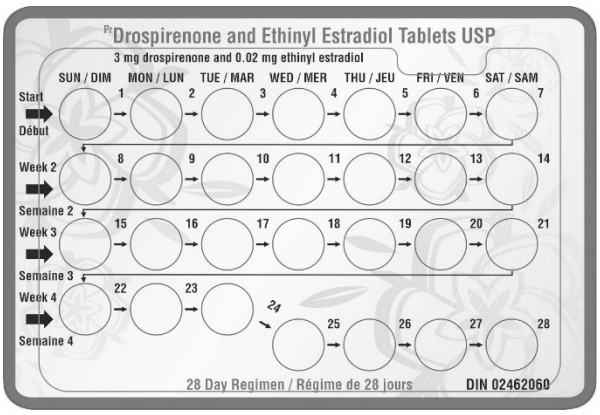
Usual dose:

HOW TO TAKE DROSPIRENONE AND ETHINYL ESTRADIOL TABLETS USP

1. **READ THESE DIRECTIONS**
   - before you start taking your pills, and
   - any time you are not sure what to do.

2. **LOOK AT YOUR PILL PACK,** it has 28 pills;

   The Drospirenone and Ethinyl Estradiol Tablets USP pill pack has 24 hormone-containing brown to reddish brown "active" pills to be taken for 24 days, followed by 4 hormone-free white to off-white "reminder" pills to be taken for four days.



   ALSO CHECK the pill pack for: 1) where to start and 2) direction to take pills in (follow the arrows).

3. You should use a second method of birth control (eg, latex or polyurethane condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a backup in case pills are forgotten while you are getting used to taking them.

4. **When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**

5. **IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES**, such as antibiotics, your pills may not work as well. Use a back-up method, such as latex or polyurethane condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

6. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

7. Take the pills only on the advice of your doctor and carefully follow all directions given to you. You must take the pills exactly as prescribed. Otherwise, you may become pregnant.

8. Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.

9. **THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.**

10. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS BE SURE TO READ THESE INSTRUCTIONS:

- before you start taking your pills, and
- any time you are not sure what to do.

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills. Pick a time of day which will be easy to remember.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1 or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS**. Your period should occur during the last four days of using that pill pack.

WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**

- Try to associate taking your pill with some regular activity, such as eating a meal or going to bed.
- Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
- Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK**

Start the next pack on the day after your last hormone-free white to off-white "reminder" pill. Take one pill every day. Do not wait any days between packs.

Overdose:

Symptoms of overdose may include nausea, vomiting, or vaginal bleeding. Even girls who have not yet had their first menstrual period but have accidentally taken this medicine may experience such bleeding. Available information from cases of accidental ingestion of oral contraceptives by children indicates no serious effects.

If you think you, or a person you are caring for, have taken too much Drospirenone and Ethinyl Estradiol Tablets USP, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

MISSING PILLS CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING, even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.

IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:

- when you start a pack late, or
- when you miss pills at the beginning or at the very end of the pack.

WHAT TO DO IF YOU MISS PILLS

The following chart outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

Sunday Start	**Other Than Sunday Start**
Miss One Brown to Reddish Brown Pill At Any Time	**Miss One Brown to Reddish Brown Pill At Any Time**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
Miss Two Brown to Reddish Brown Pills in a Row	**Miss Two Brown to Reddish Brown Pills in a Row**
First Two Weeks: 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.	**First Two Weeks:** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.
Third and Fourth Week 1. Keep taking one pill a day until Sunday.	**Third and Fourth Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day.

2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**
Miss Three or More Brown to Reddish Brown Pills in a Row	**Miss Three or More Brown to Reddish Brown Pills in a Row**
Anytime in the Cycle 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Anytime in the Cycle** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

NOTE: If you forget any of the four hormone-free white to off-white "reminder" pills in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand

- a backup method of birth control (such as latex or polyurethane condoms and spermicidal foam or gel) in case you miss pills, and an extra, full pack of pills.

IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC about ways to make pill-taking easier or about using another method of birth control.

Noncontraceptive Benefits of Birth Control Pills

Several health advantages have been linked to the use of birth control pills:

- Combination estrogen and progestin birth control pills reduce the incidence of cancer of the uterus and ovaries.
- Birth control pills reduce the likelihood of developing benign (noncancerous) breast disease and ovarian cysts.
- Users of birth control pills lose less menstrual blood and have more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and in premenstrual syndrome (PMS).
- Acne, excessive hair growth, and male hormone-related disorders also may be improved.
- Ectopic (tubal) pregnancy may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been observed in studies of women taking Drospirenone and Ethinyl Estradiol Tablets USP which may or may not be drug related:

Most side effects when using the birth control pill are not serious. The most common side effects are nausea, vomiting, bleeding or spotting between menstrual periods, breast pain, acne, itching, migraine, dizziness, emotional lability (sudden changes in emotional state without a reason), dysmenorrhea (painful menstrual cramps), headache, vaginal yeast infection, depression, back pain, abdominal pain, nervousness, rash.

Other side effects can occur such as gastrointestinal symptoms (abdominal cramps and bloating), darkening of the skin (particularly on the face), change in appetite, change in libido (sex drive), hair loss, change in weight (increase or decrease), swelling, breast changes (tenderness, enlargement, discharge), temporary infertility after discontinuation of treatment.

If you experience new onset of high blood pressure or worsening of high blood pressure, contact your doctor or pharmacist.

The following additional symptoms have been reported in women taking hormonal contraceptives in general:

- difficulty wearing contact lenses
- vaginal irritation or infections
- urinary tract infections or inflammation
- upper respiratory tract infections (colds, bronchitis, runny or stuffy nose, sore throat, etc.)
- severe headaches
- depression, insomnia, nervousness
- amenorrhea (lack of a period or breakthrough bleeding)
- back pain
- abdominal pain
- flu-like symptoms
- allergy, fatigue, fever
- diarrhea, flatulence
- rash

Many women have spotting or light bleeding or may feel sick to their stomach during the first three months on the pill. If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

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

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Abdominal pain, nausea or vomiting or lump in the abdomen		√	
Breast lump		√	
Crushing chest pain or heaviness			√
Pain or swelling in the leg			√
Persistent sad mood			√

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

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Sharp pain in the chest, coughing blood, or sudden shortness of breath			√
Sudden partial or complete loss of vision or double vision			√
Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg.			√
Unexpected vaginal bleeding		√	
Unusual swelling of the extremities		√	
Yellowing of the skin or eyes (jaundice)			√

This is not a complete list of side effects. For any unexpected effects while taking Drospirenone and Ethinyl Estradiol Tablets USP, contact your doctor or pharmacist.

HOW TO STORE IT

Store in original packaging between 15ºC and 30ºC. Keep out of reach of children and pets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Reporting Side Effects:

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Drospirenone and Ethinyl Estradiol Tablets USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by calling 1-844-801-7468.

This leaflet was prepared by:

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