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Product Monograph

Including Patient Medication Information

Pr ZAMINE® 21

Pr ZAMINE® 28

Drospirenone and Ethinyl Estradiol Tablets

For Oral use

3 mg drospirenone and 0.03 mg ethinyl estradiol

USP

Oral Contraceptive

Acne Therapy

APOTEX INC.
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Toronto, Ontario
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Date of Authorization: 2026-02-13

Control Number: 301439

Recent Major Label Changes

None at the time of the most recent authorization.

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Health Professional Information

1. Indications

ZAMINE (drospirenone and ethinyl estradiol tablets) is indicated for:

- Conception Control
- Treatment of moderate acne vulgaris in women ≥ 16 years of age who have no known contraindications to oral contraceptive therapy, desire contraception, and have achieved menarche

1.1. Pediatrics

Pediatrics (< 16 years of age): The safety and efficacy of drospirenone and ethinyl estradiol tablets has not been established in women under the age of 16 years. Use of this product before menarche is not indicated (see 7.1.3. Pediatrics).

1.2. Geriatrics

Geriatrics: ZAMINE is not indicated for use in postmenopausal women. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2. Contraindications

ZAMINE 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
- history of or actual prodromi of a thrombosis (e.g., 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 7. Hepatic/Biliary/Pancreatic)

- 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 6. Dosage Forms, Strengths, Composition, and Packaging.

3. Serious Warnings and Precautions Box

- 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 contraceptives, including ZAMINE, should not be used by women who are over 35 years of age and smoke. Women should be counselled not to smoke (see 7. Cardiovascular).

- 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.

4. Dosage and Administration

4.2. Recommended Dose and Dosage Adjustment

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

It is recommended that ZAMINE tablets should be taken every day at about the same time regardless of mealtimes and as directed on the package.

4.4. Administration

Conception Control

Tablets must be taken in the order directed on the package every day at about the same time. The patient may begin using ZAMINE on Day 1 of her menstrual cycle (i.e., the first day of menstrual flow), on Day 5, or on the first Sunday after her period begins. If the patient's period begins on Sunday, she should start that same day. If ZAMINE tablets are taken later than Day 1 when first starting medication, an additional (barrier) method of birth control is recommended for the first seven days of use.

ZAMINE 21 (21-Day Regimen)

One hormone-containing yellow tablet is to be taken daily for 21 consecutive days. Tablets are then discontinued for 7 consecutive days. Withdrawal bleeding usually occurs within 2 to 3 days following discontinuation.

The patient begins each subsequent course of ZAMINE 21 tablets on the same day of the week that she began her first course. She begins taking her next course on the 8th day after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

ZAMINE 28 (28-Day Regimen)

One hormone-containing yellow tablet is to be taken daily for 21 consecutive days, followed by one hormone-free white tablet daily for 7 consecutive days. Withdrawal bleeding usually occurs within 2 to 3 days following the last hormone-containing yellow tablet (i.e., while the patient is taking the hormone-free white tablets).

The patient begins each subsequent course of ZAMINE 28 tablets 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. There is no need for the patient to count days between cycles because there are no "off-tablet days."

Acne

The timing of initiation of ZAMINE 21 and ZAMINE 28 treatment for acne should follow the instructions for use of ZAMINE 21 and ZAMINE 28 for contraception (see 4.4. Conception Control).

Special Notes on Administration

Switching from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch)

The patient should start ZAMINE 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 ZAMINE preferably on the day of removal, but at the latest when the next application would have been due.

Switching from a progestogen-only method (mini-pill, injection) or from a Progestogen-releasing Intrauterine System (IUS)

The patient may switch from the mini-pill to ZAMINE on any day of her cycle. Patients using a progestogen injection should start ZAMINE on the day the next injection is due. Patients using an IUS should start ZAMINE 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 ZAMINE use.

Following first trimester abortion

The patient may start using ZAMINE immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second trimester abortion

Patients should be advised to start ZAMINE 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 seven days of ZAMINE 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 ZAMINE. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (see 7.1.2. Breastfeeding).

Withdrawal / Breakthrough bleeding

Withdrawal bleeding usually occurs within 3 days following the last hormone-containing yellow tablet. If spotting or breakthrough bleeding occurs while taking ZAMINE, the patient should be instructed to continue taking ZAMINE as instructed 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 ZAMINE is 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 one 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.

4.5. Missed Dose

The patient should be instructed to use the following chart if she misses one 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 yellow tablet missed.

Table 1 – Management of Missed Hormone-Containing Yellow Tablets

<table>
<tr><th>Sunday Start</th><th>Other Than Sunday Start</th></tr>
<tr><td colspan="2">Miss One Yellow Tablet At Any Time</td></tr>
<tr><td colspan="2">Take the missed pill 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.</td></tr>
<tr><td colspan="2">Miss Two Yellow Tablets in a Row</td></tr>
<tr><td colspan="2">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.</td></tr>
<tr><td>Third Week
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 your period this month.

If you miss two periods in a row, call your healthcare professional or clinic.</td><td>Third Week
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 tablets.
3. You may not have your period this month.

If you miss two periods in a row, call your healthcare professional or clinic.</td></tr>
<tr><td colspan="2">Miss Three or More Yellow Tablets in a Row</td></tr>
<tr><td>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 your period this month.

If you miss two periods in a row, call your healthcare professional or clinic.</td><td>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 tablets.
3. You may not have your period this month.

If you miss two periods in a row, call your healthcare professional or clinic.</td></tr>
</table>

Patients taking ZAMINE 28: If the patient forgets any of the seven hormone-free white tablets in Week 4, she should be advised to safely dispose of the tablets she missed, and then to keep taking one tablet each day until the pack is empty. A back-up method of birth control is not required.

5. Overdose

There have been no reports of overdose with drospirenone and ethinyl estradiol tablets. 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669)**.**

6. Dosage Forms, Strengths, Composition, and Packaging

Table 2 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-Medicinal Ingredients
Hormone-containing yellow tablet		
Oral	Tablet / 3 mg drospirenone and 0.03 mg ethinyl estradiol	Corn starch, crospovidone (Polyplasdone XL), crospovidone (Polyplasdone XL-10), iron oxide yellow (e172), lactose monohydrate, macrogol 3350 (polyethylene glycol), magnesium stearate, polysorbate 80 (Tween 80), polyvinyl alcohol-partial hydrolyzed, povidone K-30, pregelatinized starch, talc and titanium dioxide (E171).
Hormone-free white tablet		
Oral	No active ingredient	Lactose anhydrous, macrogol 3350 (polyethylene glycol), magnesium stearate, polyvinyl alcohol-partial hydrolyzed, povidone K-30, talc, and titanium dioxide (E171).

ZAMINE (drospirenone and ethinyl estradiol) tablets are available in a 21-day regimen (ZAMINE 21) and a 28-day regimen (ZAMINE 28) in blister packs.

ZAMINE 21

Each blister pack contains 21 hormone-containing round, yellow film-coated tablets with ZY and 17 debossed on opposite sides.

Each hormone-containing yellow, film-coated tablet contains 3.0 mg drospirenone and 0.030 mg ethinyl estradiol.

ZAMINE 28

Each blister pack contains 21 hormone-containing round, yellow film-coated tablets with ZY and 17 debossed on opposite sides, and 7 hormone-free plain, round, white, film coated tablets.

Each hormone-containing yellow, film-coated tablet contains 3.0 mg drospirenone and 0.030 mg ethinyl estradiol.

The white tablets are hormone-free.

7. Warnings and Precautions

Please see 3. Serious Warnings and Precautions Box.

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** (e.g., 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 7. Perioperative Considerations.

C. **Visual defects - partial or complete**

D. **Papilledema, or ophthalmic vascular lesions**

E. **Severe headache of unknown etiology or worsening of preexisting 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, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), sickle cell disease, valvular heart disease and atrial fibrillation.

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, systemic lupus

erythematosus, hemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, and otosclerosis-related hearing loss.

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 progestogens than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestogen administered orally remains to be determined.

ZAMINE contains 3 mg of the progestogen drospirenone (DRSP) that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. ZAMINE should not be used in patients with conditions that predispose to hyperkalemia (i.e., 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.

Carcinogenesis and Genotoxicity

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 OC users. As breast cancer is rare in women under 40 years of age, the excess number is small in relationship 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 a 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, e.g., 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 16. Non-Clinical 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 ZAMINE, 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.

Driving and Operating Machinery

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

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 2. 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.

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.

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 two- to three-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. 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. 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. These retrospective studies suggest a potential 1.5 to 3 times risk of VTE in users of drospirenone-containing COCs. Epidemiological studies have inherent methodological issues making the interpretation of their results complex. 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 (e.g., 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 (e.g., “shortness of breath”, “coughing”) are nonspecific and might be misinterpreted as more common or less severe events (e.g., 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 (ATE) 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 tablets, a contributory role of drospirenone and ethinyl estradiol tablets could not be ruled out. ZAMINE is contraindicated in patients with active liver disease (see 2. Contraindications and 9.7. 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 with 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

ZAMINE must be discontinued prior to starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see 2. Contraindications and 9. 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. ZAMINE 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.

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 (e.g., 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 three 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.

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 2. 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.

Perioperative 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 one 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.

Reproductive Health

- **Fertility**

After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one 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 six 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, gastro-intestinal disturbances, or concomitant medication (see 4. Dosage and Administration and 9. 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.

7.1. Special Populations

7.1.1. Pregnancy

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with ZAMINE, 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. A causal association with drospirenone and ethinyl estradiol tablets is unknown.

7.1.2. Breastfeeding

In breastfeeding 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, 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.

7.1.3. Pediatrics

The safety and efficacy of drospirenone and ethinyl estradiol tablets has not been established in women under the age of 16 years. Use of this product before menarche is not indicated.

7.1.4. Geriatrics

ZAMINE is not indicated for use in postmenopausal women.

8. Adverse Reactions

8.1. Adverse 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 (e.g., retinal thrombosis)

- pulmonary embolism
- thrombophlebitis

The following other 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
- ulcerative colitis
- urticaria
- vaginal candidiasis
- vaginal discharge
- vaginitis

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

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following are the most common adverse events reported with use of drospirenone and ethinyl estradiol tablets during clinical trials, occurring in >1% of subjects and which may or may not be drug related: headache, menstrual disorder, breast pain, abdominal pain, nausea, leukorrhea, flu syndrome, acne, vaginal moniliasis, depression, diarrhea, asthenia, dysmenorrhea, back pain, infection, pharyngitis, intermenstrual bleeding, migraine, vomiting, dizziness, nervousness, vaginitis, sinusitis, cystitis, bronchitis, gastroenteritis, allergic reaction, urinary tract infection, pruritus, emotional lability, surgery, rash, upper respiratory infection.

8.3. Less Common Clinical Trial Adverse Reactions

Other reactions to oral contraceptives, as a general rule, are seen less frequently or only occasionally, as follows: gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuation of treatment, edema, chloasma or melasma which may persist, breast changes (tenderness, enlargement, secretion), change in weight (increase or decrease), endocervical hyperplasias, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, premenstrual-like syndrome, intolerance to contact lenses, change in corneal curvature (steepening), cataracts, optic neuritis, retinal thrombosis, changes in libido, chorea, changes in appetite, cystitis- like syndrome, rhinitis, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function, Raynaud's phenomenon, auditory disturbances, hemolytic uremic syndrome, pancreatitis.

8.5. Post-Market Adverse Reactions

Cumulative postmarketing experience with drospirenone and ethinyl estradiol tablets indicates a spontaneous reporting rate of venous thromboembolism of 5.1 events per 100000 woman-years.

The following serious and unexpected adverse reactions have also been reported very rarely in users of drospirenone and ethinyl estradiol tablets, but a causal relationship has not been established: pancytopenia, thrombocytopenia, arrhythmia, palpitations, tachycardia, ventricular extrasystoles, sudden hearing loss, ocular hypertension, visual disturbance, vitreous opacities, ischaemic colitis, hepatitis, hyperbilirubinemia, abnormal liver function test, decreased blood sodium, bone pain, pain in extremity, fibroadenoma of breast, seizure, dysarthria, facial paresis, hemiparesis, hypoesthesia, syncope, anxiety, nervousness, panic reaction, breast cyst, hematometra due to cervical polyp, asthma, leukocytoclastic vasculitis, lichen planus, and petechiae.

Cases of erythema nodosum, erythema multiforme, and hypersensitivity (including symptoms such as rash, urticaria) have been reported as adverse drug reactions from postmarket reporting in association with the use of drospirenone and ethinyl estradiol tablets.

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 ADRs from postmarketing experience reported in association with the use of drospirenone and ethinyl estradiol tablets (see 2. Contraindications and 7. 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.

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

Post-Market Active Surveillance Study

A prospective, controlled, noninterventional, active surveillance cohort study (EURAS) was conducted in Europe to compare risks of adverse cardiovascular and other events associated with the use of DRSP-containing OCs (drospirenone and ethinyl estradiol tablets) and other OCs. In this study, 58,674 OC users were actively followed for a total of 142,475 woman-years. Loss to follow-up was 2.4%. The hazard ratios for venous thromboembolic (VTE) and for all thromboembolic (TE) events were close to 1 and thus do not suggest a higher risk for drospirenone and ethinyl estradiol tablets users. The results exclude a 1.5 fold thromboembolic risk of drospirenone and ethinyl estradiol tablets users compared to users of LNG-containing OCs and a 1.2-fold thromboembolic risk compared to users of other OCs. Arrhythmic events that could be suggestive of an increased serum potassium level (e.g., because of the antimineralocorticoid activity of DRSP) were not observed in this Postmarket Surveillance study.

Hazard ratios and confidence limits for VTE, ATE and TE are presented below in Table 3.

Table 3 – Adjusted Hazard Ratios (HR) and Confidence Limits for VTE, ATE and TE (As Treated Analysis)

	Drospirenone and ethinyl estradiol tablets vs.					
	LNG-containing OCs		Other OCs		LNG and Other OCs	
	HR	95% CI	HR	95% CI	HR	95% CI
VTE	1.05	0.61 – 1.81	0.77	0.48 – 1.26	0.87	0.55 – 1.37
ATE	0.25	0.05 – 1.17	0.34	0.08 – 1.52	0.30	0.07 – 1.29
TE[a]	0.85	0.51 – 1.42	0.69	0.44 – 1.12	0.76	0.49 – 1.17

Abbreviations: ATE = arterial thromboembolism, CI = confidence interval, LNG = levonorgestrel, OC = oral contraception, TE = thromboembolic event, VTE = venous thromboembolism

a All thromboembolic events (VTE and ATE combined)

9. Drug Interactions

9.2. 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.

9.3. Drug-Behaviour Interactions

See 7. Driving and Operating Machinery. No studies on the effects of drospirenone and ethinyl estradiol tablets on the ability to drive or use machines have been performed.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

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 two hours apart.
Antibiotics	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

Class of Compound	Drug	Proposed Mechanism	Suggested Management
			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	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	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.

Class of Compound	Drug	Proposed Mechanism	Suggested Management
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 contraception or higher dose oral contraceptives.
Other drugs	Antihistamines Analgesics 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 tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

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

Several of the anti-HIV/HCV protease inhibitors (e.g., ritonavir, telaprevir, boceprevir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine) have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase or decrease) in the mean AUC of the estrogen or progestogen have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare professionals 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 (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., 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 7. General).

Oral contraceptives may also interfere with the metabolism of other drugs (see Table 5). Accordingly, plasma and tissue concentrations may either increase (e.g., cyclosporine) or decrease (e.g., 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	Fluid retention 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	Isoproterenol	Estrogen causes decreased	Adjust dose of drug as necessary. Discontinuing oral

Class of Compound	Drug	Modification of Drug Action	Suggested Management
agents		response to these drugs.	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	Its 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, Ritonavir, with and without Dasabuvir	Has been shown to be associated with increases in ALT levels 5 to > 20 times the upper limit of normal in healthy female subjects and HCV infected women	See 2. Contraindications and 7. 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	Clomipramine	Increased side effects: e.g.,	Use with caution.

Class of Compound	Drug	Modification of Drug Action	Suggested Management
antidepressants	(possibly others)	depression	
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 (e.g., midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g., theophylline) or moderately (e.g., melatonin and tizanidine).

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 with other drugs (see 7. 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 (E2) 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/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

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 10.3. Pharmacokinetics). In *in vitro* studies, DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 and CYP3A4 activity was investigated in clinical pharmacokinetic studies using omeprazole, simvastatin and midazolam as marker substrates. In a 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**.**

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. 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.

9.7. 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:

Liver Function Tests

Aspartate serum transaminase (AST) - variously reported elevations.

Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated.

Coagulation Tests

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

Thyroid Function Tests

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

Lipoproteins

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

Gonadotropins

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

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.

10. Clinical Pharmacology

10.1. Mechanism of Action

Drospirenone and ethinyl estradiol is a monophasic, combination oral contraceptive that contains the active ingredients drospirenone and ethinyl estradiol. 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. 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.

Estrogen-containing combinations such as drospirenone and ethinyl estradiol increase the blood level of sex hormone binding-globulin (SHBG), which is capable of binding and thus inactivating androgens such as testosterone. Moreover, the anti-androgenic 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.

10.2. Pharmacodynamics

Drospirenone inhibits ovulation and follicular development at an oral threshold dose of 2 mg. Drospirenone 3 mg, in combination with ethinyl estradiol 0.03 mg, was found to be optimal for inhibition of ovulation and cycle control.

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 (0.03 mg). 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 (0.03 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 remained unchanged or was slightly decreased.

Drospirenone had no effect on the biosynthesis of sex hormone binding globulin (SHBG) and when administered in conjunction with ethinyl estradiol (0.03 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).

10.3. Pharmacokinetics

Table 6 – Mean Pharmacokinetic Parameters of drospirenone and ethinyl estradiol (Drospirenone 3 mg and Ethinyl Estradiol 0.03 mg)

Drospirenone Mean (%CV) Values					
Cycle/Day	**No. of Subjects**	**C_{max} (ng/mL)**	**t_{max} (h)**	**$AUC_{(0-24h)}$ (ng·h/mL)**	**$t_{½}$ (h)**
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)
Ethinyl Estradiol Mean (%CV) Values					
Cycle/Day	**No. of Subjects**	**C_{max} (pg/mL)**	**t_{max} (h)**	**$AUC_{(0-24h)}$ (pg·h/mL)**	**$t_{½}$ (h)**
1/1	11	53.5 (43)	1.9 (45)	280.3 (87)	NA
1/21	11	92.1 (35)	1.5 (40)	461.3 (94)	NA
6/21	11	99.1 (45)	1.5 (47)	346.4 (74)	NA
9/21	11	87.0 (43)	1.5 (42)	485.3 (92)	NA
13/21	10	90.5 (45)	1.6 (38)	469.5 (83)	NA

NA = Not available

Absorption:

The absolute bioavailability of drospirenone (DRSP) from a single entity tablet is about 76%. The absolute bioavailability of ethinyl estradiol (EE) is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of ZAMINE which is a combination

tablet of drospirenone and ethinyl estradiol has not been evaluated. Serum concentrations of DRSP and EE reached peak levels within 1 to 3 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 117% for DRSP and EE, respectively.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1 to 10 mg. Following daily dosing of drospirenone and ethinyl estradiol, steady state DRSP concentrations were observed after 10 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 (see Table 6).

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.

Effect of Food

The rate of absorption of DRSP and EE following single administration of two drospirenone and ethinyl estradiol tablets 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 sex hormone-binding globulin (SHBG) or corticosteroid-binding globulin (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 two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP, generated by opening of the lactone ring, and the 4,5-dihydrodrospirenone-3-sulfate, formed by reduction and subsequent sulfation. These metabolites were shown not to be pharmacologically active. DRSP is also subject to oxidative metabolism 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.

Elimination:

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 ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38% to 47% of the metabolites in urine were glucuronide and 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 (<16 years of age):** There is no PK data available. Use of this product before menarche is not indicated.
- **Geriatrics:** There is no PK data available. ZAMINE is not indicated for use in postmenopausal women.
- **Sex:** ZAMINE is intended for use only in women of reproductive age.
- **Pregnancy and breastfeeding:**
  - Pregnancy: ZAMINE is not indicated for use in pregnancy (see 2. Contraindications and 7.1.1. Pregnancy).
  - Breastfeeding: 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 (see 7.1.2. Breastfeeding).
- **Ethnic Origin:** The effect of race on the disposition of drospirenone and ethinyl estradiol has not been evaluated.
- **Hepatic Insufficiency:** ZAMINE is contraindicated in patients with hepatic dysfunction (see 7. Warnings and Precautions). 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.
- **Renal Insufficiency:** ZAMINE is contraindicated in patients with renal insufficiency (see 7. Renal).

  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 to 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 to 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 to 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 five of the seven

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.

11. Storage, Stability, and Disposal

Store in original packaging at controlled room temperature 15°C - 30°C.

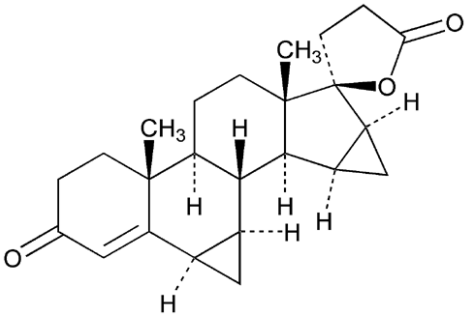
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Part 2: Scientific Information

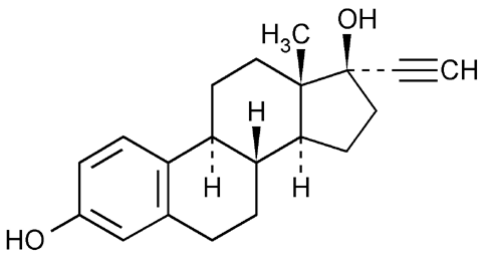
13. Pharmaceutical Information

Drug Substance

***Drospirenone**:*

Non-proprietary name of the drug substance:	Drospirenone
Chemical name:	6β, 7β; 15β, 16β-dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone (IUPAC) [6R-(6α, 7α, 8β, 9α, 10β, 13β, 14α, 15α, 16α,17β]-1,3′,4′,6, 7,8,9,10,11,12,13,14,15,16,20,21-hexadecahydro-10,13-dimethylspiro [17*H*-dicyclopropa[6,7:15, 16] cyclopenta[α]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione (USAN)
Molecular formula and molecular mass:	$C_{24}H_{30}O_3$ (366. 49 g/mol)
Structural formula:	
Description:	White to off-white crystalline powder. Freely soluble in dichloromethane; soluble in acetone, methanol, ethyl acetate, dimethoxyethane, and toluene; sparingly soluble in ethanol, and practically insoluble in water, n-hexane and diisopropyl ether. Melting range is 199°C to 201°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:

Non-proprietary name of the drug substance:	ethinyl estradiol
Chemical name:	19-nor-17α-pregna-1,3,5(10)-triene-20-yne-3,17-diol (IUPAC)
Structural formula:	
Molecular formula and molecular mass:	$C_{20}H_{24}O_2$ (296.40 g/mol)
Description:	White to yellowish-white crystals or crystalline powder. Freely soluble in ether, ethanol, acetone, and dioxane; soluble in chloroform and alkali hydroxide solutions; practically insoluble in water. Melting range is 181°C to 185°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)

14. Clinical Trials

14.1. Clinical Trials by Indication

Oral Contraception

The contraceptive efficacy of drospirenone and ethinyl estradiol tablets was demonstrated in three pivotal, open-label, multicentre, clinical trials conducted in women 16 to 40 years of age (see Table 7).

Table 7 – Contraceptive Efficacy of drospirenone and ethinyl estradiol tablets in 3 Pivotal Clinical Trials

	Study 1	Study 2	Study 3
Corrected[a] Pearl Index			
Number of cycles	3192	18418	9490
Number of pregnancies	1	10	3
Pearl Index	0.41	0.71	0.41
Corrected[a] Pregnancy Ratio			
Cycles completed/subject	13	13	26
Number of subjects	220	1186	268
Number of pregnancies	1	10	3
Pregnancy Ratio (%)	0.46	0.84	1.18

a Corrected to exclude concomitant use of other contraceptives

Of the 14 on-treatment pregnancies reported for drospirenone and ethinyl estradiol tablets, there were 11 cases in which co factors (missed tablets, diarrhea, etc) were identified that could have reduced the contraceptive efficacy. These cases may be accepted as user failures.

Acne Therapy

The efficacy of drospirenone and ethinyl estradiol tablets in treating moderate acne was demonstrated in two pivotal, double blind, comparative, multicentre clinical trials in women 16 to 40 years of age.

Study A07158

The primary objectives of the study were to compare the efficacy of drospirenone and ethinyl estradiol tablets with a triphasic preparation containing 0.035 mg ethinyl estradiol and 0.180, 0.215, 0.250 mg norgestimate (EE/NGM), in terms of relative change in inflammatory lesion count in percent (papules + pustules + nodules), relative changes in total lesion count in percent (papules + pustules + nodules + open and closed comedones), and the proportion of subjects who showed improvement of their facial acne according to the investigator's global assessment from randomization to Cycle 6.

Female subjects were randomized to drospirenone and ethinyl estradiol tablets (n = 568) or EE/NGN (n = 586) for 6 treatment cycles.

The relative change (reduction) from baseline to Cycle 6 in mean percentage inflammatory lesion count was 73.4% for drospirenone and ethinyl estradiol tablets vs 71.0% in EE/NGM (*P* value of one-sided t-test for noninferiority is smaller than 0.001) for the full analysis set population.

The relative change (reduction) from baseline to Cycle 6 in the mean percentage total lesion count was 67.6% in drospirenone and ethinyl estradiol tablets and 64.3% in EE/NGM for the full analysis set population.

For the investigator's global assessment, improvement of facial acne was observed in subjects treated with drospirenone and ethinyl estradiol tablets (95.6%) vs EE/NGM (92.1%) for the full analysis set population.

The per protocol analysis showed similar results to the full analysis set.

Study AM80

This multicentre, double-blind, randomized study compared the effect of drospirenone and ethinyl estradiol tablets with that of 0.035 mg ethinyl estradiol/2 mg cyproterone acetate (EE/CPA). The study was completed over 9 treatment cycles. A total of 128 women with acne (aged 16 to 33 with a minimum of 8 papulopustular lesions on the face) were randomized. Treatment with either drospirenone and ethinyl estradiol tablets (n = 82) or EE/CPA (n = 43) was assigned in a 2:1 ratio. Acne lesion count was assessed as the primary variable. After nine treatment cycles, the mean number of acne lesions was reduced by 37.51% in the drospirenone and ethinyl estradiol tablets group and 35.03% in the EE/CPA group in the intent-to-treat (ITT) population (*P* value from Wilcoxon test = 0.0006).

The per protocol analysis showed similar results to the ITT analysis.

14.2. Comparative Bioavailability Studies

A randomized, two-way crossover, single oral dose (6.0 mg/0.06 mg dose as 2 x 3.0 mg/0.03 mg) comparative bioavailability study of ZAMINE tablets, 3.0 mg/0.03 mg (manufactured by Leon Farma Laboratories, S.A. for Apotex Inc.) and ^{Pr}YASMIN® 21 tablets, 3.0 mg/0.03 mg (Bayer Inc, Canada) was conducted in healthy adult Asian female subjects under fasting conditions. Comparative bioavailability data from the 16 subjects that were included in the statistical analysis for Drospirenone and Ethinyl Estradiol are presented in the following tables:

Table 8 - Summary Table of the Comparative Bioavailability Data

Drospirenone (2 x 3.0 mg/0.03 mg drospirenone /ethinyl estradiol) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of geometric means**	**90% Confidence Interval**
$AUC_{0\text{-}72h}$ (ng·h/mL)	921.30 952.30 (23.17)	911.95 932.15 (20.72)	101.0	97.5 – 104.7
C_{max} (ng/mL)	66.55 68.44 (21.29)	70.89 71.73 (17.24)	93.9	85.4 – 103.2
T_{max}[3]	1.42	1.50		

Drospirenone (2 x 3.0 mg/0.03 mg drospirenone /ethinyl estradiol) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of geometric means**	**90% Confidence Interval**
(h)	(1.00 – 3.00)	(1.00 – 5.02)		

[1] ZAMINE (drospirenone/ ethinyl estradiol) tablets, 3.0 mg/0.03 mg (manufactured by Leon Farma Laboratories, S.A. for Apotex Inc.).
[2] PrYASMIN® 21 (drospirenone/ ethinyl estradiol) tablets, 3.0 mg/0.03 mg (Bayer Inc., Canada).
[3] Expressed as the median (range) only.
Due to the long elimination half-life of Drospirenone, AUC_I and $T_{½}$ could not be accurately calculated from the data obtained in this study.

Table 9 - Summary Table of the Comparative Bioavailability Data

Ethinyl Estradiol (2 x 3.0 mg/0.03 mg drospirenone /ethinyl estradiol) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of geometric means**	**90% Confidence Interval**
AUC_T (pg·h/mL)	1352.90 1449.80 (37.66)	1340.55 1421.51 (34.90)	100.9	96.5 – 105.6
AUC_I (pg·h/mL)	1403.66 1507.08 (38.53)	1383.96 1469.99 (35.54)	101.4	97.2 – 105.8
C_{max} (pg/mL)	125.68 132.70 (31.52)	130.86 138.22 (33.29)	96.0	90.8 – 101.6
T_{max}[3] (h)	2.00 (1.25 – 2.52)	1.75 (1.00 – 3.00)		
$T_{1/2}$[4] (h)	14.91 (23.16)	14.58 (17.71)		

[1] ZAMINE (drospirenone/ ethinyl estradiol) tablets, 3.0 mg/0.03 mg (manufactured by Leon Farma Laboratories, S.A. for Apotex Inc.).
[2] PrYASMIN® 21 (drospirenone/ ethinyl estradiol) tablets, 3.0 mg/0.03 mg (Bayer Inc., Canada).
[3] Expressed as the median (range) only.
[4] Expressed as the arithmetic mean (CV %) only.

16. Non-Clinical Toxicology

General 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 10 – 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	
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.

Genotoxicity

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 three compound-related DNA adducts were also observed in the livers of female mice given drospirenone 10 mg/kg/day, alone or in combination with 0.1 mg/kg/day ethinyl estradiol, in the carcinogenicity study. In contrast to these findings observed in rodent livers, results from an *in vitro* study conducted with drospirenone 5 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.

Carcinogenicity

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

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, i.e, 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.

Reproductive and developmental toxicology:

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

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 (e.g., 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 drospirenone and ethinyl estradiol tablets.

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.

17. Supporting Product Monographs

1. YASMIN® 21 and YASMIN® 28 (Tablets, 3.0 mg drospirenone and 0.030 mg ethinyl estradiol), control 290097, product monograph, Bayer Inc. (2025-07-07).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr ZAMINE® 21

Pr ZAMINE® 28

Drospirenone and Ethinyl Estradiol Tablets

This Patient Medication Information is written for the person who will be taking **ZAMINE**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication if you have more questions about this medication or want more information about **ZAMINE**, talk to a healthcare professional.

Serious warnings and precautions box

- Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age particularly in women older than 35 years of age, who use hormonal birth control. The risk also increases with the number of cigarettes smoked. For this reason, women who smoke and are over 35 years of age should not use ZAMINE.
- 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 AND take your birth control pills.

What ZAMINE is used for:

- To prevent pregnancy
- To treat moderate acne in women 16 years of age and older who are able to use birth control pills and have had their first menstrual period

How ZAMINE works:

Preventing Pregnancy

ZAMINE is a birth control pill (oral contraceptive). It is considered to be a combination oral contraceptive. This is because it contains two female sex hormones: drospirenone and ethinyl estradiol.

ZAMINE works in two ways:

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

Acne Treatment

ZAMINE lowers androgen levels in the body. Androgens can cause glands in the skin to over-produce oil. This results in acne. ZAMINE works by blocking the effects of androgens at the gland.

Effectiveness of Combination 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

There are other methods of birth control available. These 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 lists pregnancy rates for different types of birth control, including no birth control. A pregnancy rate is 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.

The ingredients in ZAMINE are:

Medicinal ingredients: drospirenone and ethinyl estradiol

Non-medicinal ingredients:

- Yellow (hormone-containing) tablets: Corn starch, crospovidone (Polyplasdone XL), crospovidone (Polyplasdone XL-10), iron oxide yellow (E172), lactose monohydrate, macrogol 3350 (polyethylene glycol), magnesium stearate, polysorbate 80 (Tween 80), polyvinyl alcohol-partial hydrolyzed, povidone K-30, pregelatinized starch, talc and titanium dioxide (E171).
- White (hormone-free) tablets: Lactose anhydrous, macrogol 3350 (polyethylene glycol), magnesium stearate, polyvinyl alcohol-partial hydrolyzed, povidone K-30, talc and titanium dioxide (E171).

ZAMINE comes in the following dosage forms:

- Yellow tablets: 3 mg drospirenone and 0.03 mg ethinyl estradiol
- White (hormone-free) tablets: no medicinal ingredient

ZAMINE tablets are available in a 21-day regimen (ZAMINE 21) and a 28-day regimen (ZAMINE 28).

Do not use ZAMINE if you:

- have or have had blood clots in the legs, lungs, eyes, or elsewhere in your body
- have or have had inflammation or swelling of the veins
- have or have had a stroke or heart attack
- have or have had conditions that affect blood flow to your brain
- have or have had coronary artery disease (for example, chest pain) or a condition that may be a first sign of a stroke (such as a transient ischemic attack or small reversible stroke)
- have or have had a disease of the heart valves with complications
- have severe or multiple health conditions that put you at greater risk of developing blood clots in your veins or arteries, such as if you:
  - have or have had severe high blood pressure
  - have inherited or developed issues with your blood clotting system. For example, Factor V Leiden mutation.
  - have or have had diabetes with complications
  - have or have had very high blood cholesterol or triglyceride levels
  - smoke and are over age 35
  - have or have had migraine headaches
  - are scheduled for major surgery
  - are or were on prolonged bed rest
- are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C. Using these drugs at the same time as ZAMINE has the potential to cause liver problems.
- have or have had jaundice (yellowing of the eyes or skin)

- have liver disease or liver tumor
- have or have had known or suspected cancer of the breast, uterus (womb) or other estrogen-dependent cancer
- have or have had unusual vaginal bleeding without a known reason
- have or have had loss of vision due to blood vessel disease of the eye
- are or think you might be pregnant
- have or have had inflammation of the pancreas and high levels of fat in your blood
- have kidney disease
- have adrenal disease
- are allergic to drospirenone, ethinyl estradiol, or to any of the other ingredients in ZAMINE or its container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZAMINE. Talk about any health conditions or problems you may have, including if you:

- smoke
- are overweight
- have a history of breast disease (for example, breast lumps) or a family history of breast cancer
- have a family history of blood clots, heart attacks or strokes
- have diabetes
- have heart disease
- have a history of seizures / epilepsy
- have a history of depression
- wear contact lenses
- have uterine fibroids (benign tumors of the uterus)
- are breastfeeding
- have systemic lupus erythematosus
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have hemolytic 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

Other warnings you should know about:

- **Check-ups and testing:**
  - You will have regular visits with your healthcare professional while taking ZAMINE.

    They may:

    - Do blood tests to check your potassium level. This should be done during the first month that you take ZAMINE.
    - Check your blood pressure.
    - Do a breast, liver, abdominal and a pelvic exam, including a Pap smear.
  - You should visit your healthcare professional three months or sooner after the initial examination. Afterward, visit your healthcare professional at least once a year.
  - Tell your healthcare professional if you are scheduled for any laboratory tests since certain blood tests may be affected by ZAMINE.
- **Surgery:**
  - Tell your healthcare professional if you are scheduled for major surgery. You should talk to your healthcare professional about stopping the use of ZAMINE one month before surgery and not using ZAMINE for a time period after surgery or during bed rest.
  - If you see a different healthcare professional, inform them that you are using ZAMINE.
- **High potassium levels in the blood:**
  - ZAMINE is a birth control pill containing estrogen and progestogen. The progestogen in ZAMINE is known as drospirenone and it may increase levels of potassium in your blood.
  - You should not take ZAMINE if you have conditions that can alter the body's fluid and mineral balance (such as kidney, liver, or adrenal disease). This can cause serious heart and health problems.
  - Other medicines may also increase potassium. **See The following may interact with ZAMINE**, below, for a list of medicines that can affect your potassium levels.
- **Skin problems:**
  - ZAMINE can cause chloasma gravidarum (gray-brown patches on face). It is more likely to happen if you have previously had chloasma gravidarum.
  - Avoid exposure to the sun or ultraviolet light while taking ZAMINE if you have a history of developing this skin condition.
- **Pregnancy and breastfeeding:**
  - **Use in pregnancy**
    - Do not take ZAMINE if you are pregnant.
    - Talk to your healthcare professional right away if you become or think you might be pregnant while using ZAMINE. There are specific risks you should discuss with your healthcare professional.

- **Use while breastfeeding**
  - You should avoid ZAMINE if you are breastfeeding.
  - The hormones in ZAMINE are known to appear in breast milk. This may cause yellowing of the skin and enlarged breast to develop in your child. These hormones also may decrease the amount and quality of your breast milk.
  - Talk to your healthcare professional about other methods of birth control that may be right for you.
- **Use after pregnancy, miscarriage, or an abortion**
  - Your healthcare professional will decide when you can start taking ZAMINE after childbirth, miscarriage, or abortion.
- **Pregnancy after stopping ZAMINE**
  - You should have a menstrual period when you stop using ZAMINE. Wait until after your next period before getting pregnant. This will help to better date the pregnancy.
  - Talk to your healthcare professional about other forms of birth control you can use during this time.

ZAMINE can cause serious side effects including:

- **Blood clot in legs, lungs, heart, eyes, or brain**
  - Drospirenone, the progestogen in ZAMINE may carry a higher risk of blood clots than some other progestogens (including levonorgestrel). You should talk to your healthcare professional about the available options.
  - The risk of clotting seems to increase with higher doses of estrogen. Your healthcare professional will make sure you use the lowest dose of estrogen as possible.
  - Women who use hormonal birth control are more likely to develop blood clots. Blood clots are the most common serious side effects of birth control pills. These blood clots can cause death or disability. The risk of developing blood clots is especially high during the first year a woman ever uses a hormonal birth control or restarts the same or a different hormonal birth control.
  - Clots can occur in many parts of the body. When they occur in blood vessel of eye, it can result in blindness or impaired vision. When they occur in a blood vessel leading to an arm or leg, it can cause damage to or loss of a limb.
  - You should be alert for symptoms and signs of serious adverse effects (see **Serious side effects and what to do about them**). Call your healthcare professional immediately if they occur.
- **Breast cancer, cervical cancer or liver tumors**
  - ZAMINE may increase the risk of developing breast cancer, cervical cancer or liver tumors. This can be life-threatening or may cause death.
  - **Breast cancer**
    - Your risk for breast cancer increases as you get older and if there is a strong history of breast cancer in the family (mother or sister).
    - Some women who use ZAMINE may be at a higher risk of breast cancer. Other factors that

may increase your risk of breast cancer includes:

- Being overweight
- Never having children
- Having your full-term pregnancy at a late age
- Using birth control for a long time (more than 8 years)
- Starting birth control at an early age

  - It is recommended that you have a yearly breast examination by a healthcare professional. Ask your healthcare professional for advice and instruction on regular self-examination of your breasts.

- **Cervical cancer**
  - You are at a higher risk of developing cervical cancer if you have persistent human papillomavirus infection (HPV).
- **Liver tumors**
  - The risk of developing liver tumors increases with duration of hormonal birth control use.
  - These tumors are extremely rare.

- **Gallbladder disease**
  - Women who use birth control pills have a higher chance of developing gallbladder disease requiring surgery within the first year of use.
  - The risk for developing gallbladder disease may double after 4 or 5 years of use.
- **Vaginal bleeding**
  - You may experience spotting or light bleeding during the first three months on ZAMINE. This is when you have bleeding from the vagina between periods. This problem will usually go away. If it does not go away, check with your healthcare professional or clinic.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZAMINE:

- medicines used for the treatment of epilepsy including primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate
- medicines used to treat tuberculosis including rifampin, rifabutin
- medicines used to treat HIV infections including ritonavir, nevirapine
- medicines used to treat bacterial infections including penicillins, tetracyclines, clarithromycin, erythromycin
- a medicine used to prevent organ rejection called cyclosporine
- medicines used to treat Hepatitis C including:
  - ombitasvir, paritaprevir, ritonavir, with or without dasabuvir

- boceprevir and telaprevir

- medicines used to treat fungal infections including griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole
- medicines used to lower cholesterol levels including clofibrate
- medicines used for the treatment of certain heart diseases or high blood pressure including diltiazem, verapamil
- medicines used to treat diabetes including insulin
- prednisone, a medicine used to treat many different conditions like asthma, allergic reactions and arthritis
- sedatives and hypnotics, medicines used to induce or maintain sleep, including benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate
- a pain medicine called meperidine
- medicines used to treat depression including clomipramine
- a medicine used to treat multiple sclerosis called tizanidine
- a medicine used to treat asthma called theophylline
- medicines that may increase your potassium levels such as:
  - Nonsteroidal anti-inflammatory drugs (NSAIDs) when taken long-term and for treatment of arthritis or other problems (for example, ibuprofen, naproxen or others)
  - Potassium-sparing diuretics (spironolactone and others) used to treat high blood pressure and fluid retention
  - Potassium supplements
  - ACE inhibitors and Angiotensin-II receptor antagonists for the treatment of high blood pressure (for example, captopril, enalapril, lisinopril, losartan, valsartan, irbesartan, or others)
  - Heparin, used to thin blood and prevent blood clots
- some nutritional supplements including vitamin B_{12}, folic acid
- antacids, used to treat heartburn. You should use it 2 hours before or after taking ZAMINE
- St. John's wort, a herbal product primarily used to treat depressive moods
- grapefruit juice
    - Certain medicines may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. ZAMINE may also interfere with the working of other medicines.

You should tell any other healthcare professional who prescribes another medicine that you use ZAMINE. They can tell you if you need to use an additional method of birth control and if so, for how long.

How to take ZAMINE:

1. **Read These Directions**
   - before you start taking your pills, and
   - any time you are not sure what to do.
2. Take exactly as directed by your healthcare professional. Check with your healthcare professional if you are not sure. Otherwise, you may become pregnant.
3. Decide with your healthcare professional or clinic what is the best day for you to start taking your first pack of pills. Your pills may be either a 21-day or a 28-day type.
4. You should use a second method of birth control (e.g., latex or polyurethane condoms and spermicidal foam or gel) for the **first 7 days** of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.
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 healthcare professional or clinic.
6. Visit your healthcare professional three months or sooner after the initial examination. Afterward, visit your healthcare professional at least once a year.
7. **When receiving any medical treatment, be sure to tell your healthcare professional that you are using birth control pills.**
8. Your healthcare professional will tell you 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 healthcare professional or clinic.**

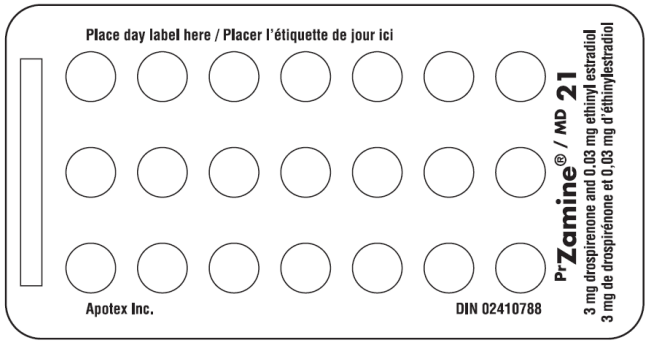
INSTRUCTIONS FOR USE

Before you start:

- **Look at your pill pack** to see if it has 21 or 28 pills.
- **Also check** the pill pack for: 1) where to start and 2) direction to take pills in (follow the arrows).

A. <u>21-Pill Pack (ZAMINE 21)</u>

21-Pill Pack: 21 hormone-containing yellow “active” pills taken daily for three weeks, and then no pills taken for one week



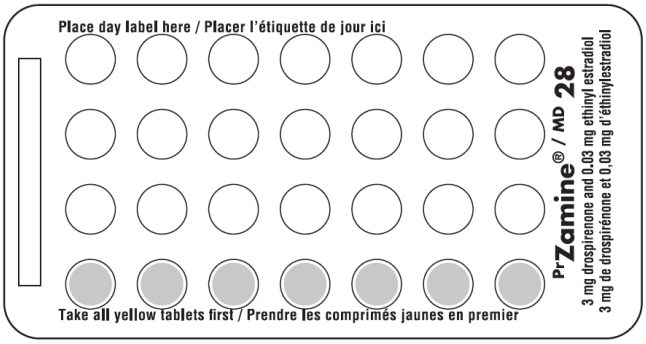
With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pills for more than seven days in a row.

Taking ZAMINE 21

1. **The first day of your menstrual period (bleeding) is day 1 of your cycle.** Your healthcare professional may advise you on when to start taking ZAMINE 21. You will need to start taking the pills on Day 1 (first day of your period), on Day 5, 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 21 days**.
    - 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.
3. The pack of pills should be finished after 21 days.
4. When you have taken all 21 pills in this pack, **wait 7 days** (take no pills during these 7 days), and then start a new pack on the eighth day. You will probably have a period during the 7 days off the pill (this bleeding may be lighter and shorter than your usual period.)

B. <u>28-Pill Pack (ZAMINE 28)</u>

28-Pill Pack: 21 hormone-containing yellow "active" pills taken daily for three weeks, and then 7 hormone-free "reminder" pills taken daily for one week.



With this type of birth control pill, you take 21 yellow pills which contain hormones and 7 white pills which contain no hormones.

Taking ZAMINE 28

1. **The first day of your menstrual period (bleeding) is day 1 of your cycle.** Your healthcare professional may advise you on when to start taking ZAMINE 28. You will need to start taking the pills on Day 1 (first day of your period), on Day 5, 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.**
   - 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
3. The pack of pills should be finished after 28 days. Your period should occur during the last 7 days of using that pill pack.
4. When you have taken all 28 pills in this pack, begin a new pack the next day, **not missing any days**. Take 1 pill every day. Do not wait any days between packs.

DIRECTIONS FOR USE OF THIS STICKER:

MON/LUN	TUE/MAR	WED/MER	THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM
TUE/MAR	WED/MER	THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN
WED/MER	THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR
THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR	WED/MER
FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR	WED/MER	THU/JEU
SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR	WED/MER	THU/JEU	FRI/VEN
SUN/DIM	MON/LUN	TUE/MAR	WED/MER	THU/JEU	FRI/VEN	SAT/SAM

Peel the sticker off for the day of the week you plan to start your pills. Place the sticker over the space provided for the days of the week and make sure it lines up with the pills. This sticker will help to remind you to take your pill every day.

Switching to ZAMINE from a different type of birth control

- If you are switching from another type of birth control, talk to your healthcare professional about when to start taking ZAMINE.

Usual dose:

21-Pill Pack (ZAMINE 21)

Take 1 tablet per day, starting with the yellow tablets. Then, when all the 21 yellow tablets are done, wait 7 days before starting a new pack.

28-Pill Pack (ZAMINE 28)

Take 1 tablet per day, starting with the yellow tablets. Then, when all the 21 yellow tablets are done, take 1 white tablet per day for 7 days.

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.

If you think you, or a person you are caring for, have taken too much ZAMINE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON (1-844-764-7669) immediately, even if there are no signs or 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 tells you what to do 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.

<table>
<tr><th>Sunday Start</th><th>Other Than Sunday Start</th></tr>
<tr><td colspan="2">Miss 1 Yellow Pill At Any Time</td></tr>
<tr><td colspan="2">Take the missed pill 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.</td></tr>
<tr><td colspan="2">Miss 2 Yellow Pills in a Row</td></tr>
<tr><td colspan="2">First Two Weeks:
1. Take 2 pills the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. Use a back-up (barrier) method of birth control if you have sex in the 7 days after you miss the pills.</td></tr>
<tr><td>Third Week
1. Keep taking 1 pill a day until Sunday.
2. On Sunday, safely discard the rest of the pack and start a new pack that day.</td><td>Third Week
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 7 days after you</td></tr>
</table>

Sunday Start	Other Than Sunday Start
3. Use a back-up (barrier) method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have your period this month. **If you miss two periods in a row, call your healthcare professional or clinic.**	miss the pills. 3. You may not have your period this month. **If you miss two periods in a row, call your healthcare professional or clinic.**
Miss 3 or More Yellow Pills in a Row	
Anytime in the Cycle 1. Keep taking 1 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 7 days after you miss the pills. 4. You may not have your period this month. **If you miss two periods in a row, call your healthcare professional 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 7 days after you miss the pills. 3. You may not have your period this month. **If you miss two periods in a row, call your healthcare professional or clinic**.

NOTE: 28-day pack - If you forget any of the 7 hormone-free white pills in Week 4, just safely discard the pills you missed. Then keep taking 1 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 1 pill two months in a row, talk to your healthcare professional or clinic about ways to make pill-taking easier or about using another method of birth control.

Possible side effects from using ZAMINE:

These are not all the possible side effects you may have when taking ZAMINE. If you experience any side effects not listed here, tell your healthcare professional.

- nausea
- vomiting
- breast pain, tenderness, enlargement, discharge
- acne
- itching
- migraine

- dizziness
- emotional lability (sudden changes in emotional state without a reason)
- painful menstrual cramps
- headache
- vaginal yeast infection
- back pain
- nervousness
- rash
- 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)
- temporary infertility after discontinuation of treatment
- difficulty wearing contact lenses
- vaginal irritation or infections
- urinary tract infections or inflammation
- upper respiratory tract infections including colds, bronchitis, runny or stuffy nose, sore throat
- insomnia
- flu-like symptoms
- allergy
- fatigue
- fever
- diarrhea
- flatulence
- excess hair on face, chest, abdomen or legs
- high blood pressure

Serious side effects and what do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Arterial thromboembolism, Myocardial infarction (blood clot in the artery, heart attack): 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; sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen			✓
Blood Clot in the Eye: Sudden partial or complete loss of vision or double vision			✓
Breast lump		✓	
Deep Vein Thrombosis (blood clot in the leg): 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			✓
Depression: Persistent sad mood			✓
Edema (fluid retention): Unusual swelling of the extremities		✓	
Jaundice: Yellowing of the skin or eyes			✓
Liver Injury: Abdominal pain, nausea or vomiting or lump in the abdomen		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Pulmonary Embolism (Blood clot in the lung): Sharp pain in the chest which may increase with deep breathing; coughing blood; sudden shortness of breath or rapid breaking; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat			✓
Stroke: Sudden severe or worsening headache or vomiting; sudden trouble walking, dizziness, loss of balance or coordination; loss of consciousness or fainting with or without seizures; sudden confusion, disturbances of vision, speech or understanding; sudden weakness or numbness of the face, arm, or leg			✓
Vaginal bleeding changes: Unexpected vaginal bleeding, bleeding or spotting between menstrual periods, lack of a period or breakthrough bleeding		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store in original packaging at controlled room temperature 15°C - 30°C. Keep the tablets in their original packaging.
- Keep out of reach and sight of children and pets.

- Do not throw away any medicines via wastewater or household waste. Ask your healthcare professional how to throw away any medicines you no longer use. These measures will help to protect the environment.

If you want more information about ZAMINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products); or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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