

Serious Warnings and Precautions

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

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

1. NAME OF THE MEDICINAL PRODUCT

YAZ Plus

3.0 mg drospirenone, 0.002 ethinyl estradiol and 0.451 levomefolate calcium tablets and 0.451 levomefolate calcium tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each blister pack contains 24 hormone-containing, pink and 4 hormone-free light-orange, film-coated, round tablets. The 4 hormone-free tablets contain folate (levomefolate calcium).

Each hormone-containing, pink, film-coated tablet contains 3.0 mg drospirenone, 0.020 mg ethinyl estradiol stabilized by betadex as a clathrate (molecular inclusion complex) and 0.451 mg levomefolate calcium.

The light-orange tablets are hormone-free and contain 0.451 mg levomefolate calcium.

Nonmedicinal ingredients for hormone-containing tablets: cellulose microcrystalline, croscarmellose sodium, ferric oxide red, hydroxypropylcellulose 5 cP, hypromellose 5 cP, lactose monohydrate, macrogol 6000, magnesium stearate, talc, titanium dioxide, β -cyclodextrin. Nonmedicinal ingredients for hormone-free tablets (containing folate): cellulose microcrystalline, croscarmellose sodium, ferric oxide red, ferric oxide yellow, hydroxypropylcellulose 5 cP, hypromellose 5 cP, lactose monohydrate, macrogol 6000, magnesium stearate, talc, titanium dioxide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Each blister pack contains 24 hormone-containing, pink and 4 hormone-free light-orange, film-coated, round tablets.

The hormone-containing tablet is round with convex faces, one side embossed with the letters "Z+" in a regular hexagon.

The hormone-free tablet is round with convex faces, one side embossed with the letters "M+" in a regular hexagon

4. CLINICAL PARTICULARS

4.1 *Therapeutic indications*

YAZ PLUS (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is indicated for:

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

4.2 *Posology and method of administration*

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

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

The patient begins each subsequent course of YAZ PLUS 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.

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

Table 1: Management of Missed Hormone-containing Pink Tablets

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

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

Special Notes on Administration

Switching from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch): The patient should start YAZ PLUS 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 YAZ PLUS preferably on the day of removal, but at the latest when the next application would have been due.

Switching from a progestin-only method (mini-pill, injection) or from a Progestin-releasing Intrauterine System (IUS): The patient may switch from the mini-pill to YAZ PLUS on any day of her cycle. Patients using a progestin injection should start YAZ PLUS on the day the next injection is due. Patients using an IUS should start YAZ PLUS 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 YAZ PLUS use.

Following first trimester abortion: The patient may start using YAZ PLUS immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second trimester abortion: Patients should be advised to start YAZ PLUS on day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the patient should be advised to use an additional (barrier) method for the first 7 days of YAZ PLUS 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 YAZ PLUS. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered.

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

Although the occurrence of pregnancy is unlikely if YAZ PLUS 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 1 or more hormone-containing tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses 2 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 pink, hormone-containing tablet is taken, absorption may not be complete. In such an event, the advice concerning management of missed tablets is applicable.

Folate Supplementation: Health Canada Prenatal Nutrition Guidelines for Health Professionals and the Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guidelines (41) recommend that women of childbearing age consume supplemental folic acid in a minimum dose of 0.4 mg (400 µg) daily. The maximum recommended daily dose of folate provided in the form of vitamin supplements for adolescents aged 14-18 years is 800 µg and for adults 19 years and older is 1000 µg. Dosages above this amount need to be administered under the supervision of a physician. Furthermore, supplementation with Vitamin B12, at the recommended dietary allowance (RDA) dose, should be considered. Consider other folate supplementation, including multivitamin intake that a woman may be taking before prescribing YAZ PLUS. Ensure that folate supplementation is maintained if a woman discontinues YAZ PLUS due to pregnancy or the desire to become pregnant.

4.3 Contraindications

YAZ PLUS should not be used in women with:

- a history of or actual thrombophlebitis or thromboembolic disorders
- a history of or actual cerebrovascular disorders
- a history of or actual myocardial infarction or coronary artery disease
- valvular heart disease with complications
- a history of or actual prodromi of a thrombosis (eg, transient ischemic attack, angina pectoris)
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis
 - severe hypertension (persistent values of $\geq 160/100$ mmHg)
 - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
 - severe dyslipoproteinemia
 - smoking, if over age 35
 - diabetes mellitus with vascular involvement
 - major surgery associated with an increased risk of postoperative thromboembolism
 - prolonged immobilization
- use with the Hepatitis C virus combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (See **WARNINGS AND PRECAUTIONS**)
- active liver disease or history of, or actual benign or malignant liver tumors
- known or suspected carcinoma of the breast
- carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- undiagnosed abnormal vaginal bleeding
- steroid-dependent jaundice, cholestatic jaundice, history of jaundice in pregnancy
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields
- known or suspected pregnancy
- current or history of migraine with focal aura
- history of or actual pancreatitis if associated with severe hypertriglyceridemia
- renal insufficiency

- hepatic dysfunction
- adrenal insufficiency
- hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION and PACKAGING** section of the Product Monograph

4.4 Special Warnings and Precautions for use

General

Discontinue Medication at the Earliest Manifestation of:

- A. Thromboembolic and Cardiovascular Disorders** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis
- B. Conditions that Predispose to Venous Stasis and to Vascular Thrombosis** (eg, immobilization after accidents or confinement to bed during long-term illness). Other nonhormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **WARNINGS AND PRECAUTIONS - Peri-operative Considerations**.
- C. Visual Defects - Partial or Complete**
- D. Papilledema, or Ophthalmic Vascular Lesions**
- E. Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache**
- F. Increase in Epileptic Seizures**

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

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity, and diabetes. Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus, 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: jaundice and/or pruritus related to cholestasis; gallstone formation, 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 progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered orally remains to be determined.

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

Carcinogenesis and Mutagenesis

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

Breast Cancer

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

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity, and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than 8 years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

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

Cervical Cancer

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

Hepatocellular Carcinoma

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

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

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, particularly in women over 35 years of age and with the number of cigarettes smoked. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke. For this reason, combination oral contraceptives, including YAZ PLUS, 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, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Hypertension

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

Endocrine and Metabolism

Diabetes

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

Lipid and Other Metabolic Effects

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

Gastrointestinal

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

Genitourinary

Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Fibroids

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

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 COC 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 µg ethinyl estradiol). The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman-years in non-pregnant, 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 COCs with low estrogen content (<50 µg ethinyl estradiol) is 2- to 3-fold higher than for nonusers of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

Several epidemiological studies have examined the risk of VTE with drospirenone-containing COCs versus other COCs. Two prospective cohort studies showed that the risk of VTE with drospirenone-containing COCs is comparable to that of other COCs, including levonorgestrel-containing COCs. 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 1.5-3 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 (eg, hepatic, mesenteric, renal, cerebral, or retinal veins and arteries) in COC users.

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

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

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

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

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

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

Other generalized risk factors for venous or arterial thromboembolism include but are not limited to age, severe obesity (body mass index >30 kg/m²), 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 2 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 YAZ[®], a contributory role of YAZ[®] could not be ruled out. YAZ PLUS is contraindicated in patients with active liver disease (see **CONTRAINDICATIONS and DRUG INTERACTIONS - Drug-Laboratory Test Interactions**).

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

Jaundice

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

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

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

Gallbladder Disease

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

Hepatic Nodules

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

Hepatitis C

YAZ PLUS must be discontinued prior to starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (See **CONTRAINDICATIONS and DRUG INTERACTIONS**). During clinical trials with ombitasvir, paritaprevir, ritonavir, with and without dasabuvir, ALT elevations 5 to >20 times the upper limit of normal (ULN) were significantly more frequent in healthy female subjects and HCV infected women using ethinyl estradiol-containing medications such as COCs. YAZ PLUS 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.

Neurologic

Migraine and Headache

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

Ophthalmologic

Ocular Disease

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

Ocular Lesions

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

Peri-operative Considerations

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

Psychiatric

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

Renal

Fluid Retention

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

Sexual Function/Reproduction

Return to Fertility

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

Amenorrhea

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

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

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

Reduced Efficacy

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

Skin

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

Special Populations

Pregnant Women

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with YAZ PLUS, further intake must be stopped and a prenatal vitamin containing folate supplementation should be initiated. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child. One infant was born with esophageal atresia during treatment with YASMIN, a COC of similar composition (ethinyl estradiol and drospirenone only) but with different dose and regimen. The causal association is unknown.

Nursing Women

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

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

After oral administration of YASMIN[®], a COC of similar composition (ethinyl estradiol and drospirenone only) but with different dose and regimen, about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 µg drospirenone in an infant.

Pediatrics

The safety and efficacy of YAZ PLUS has been established in women aged 18 and over. Use of this product before menarche is not indicated. The maximum recommended daily dose for folate supplementation in adolescents is less than that for adults (see **DOSAGE** and

ADMINISTRATION - Special Notes on Administration, Folate Supplementation)

Geriatrics

YAZ PLUS is not indicated for use in postmenopausal women.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

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

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

Folates may mask vitamin B₁₂ deficiency.

4.5 Interaction with other medicinal products and other forms of interaction

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. Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and nonprescription, before oral contraceptives are prescribed.

Drug-Drug Interactions

Table 2: Drugs Which May Decrease the Efficacy of Oral Contraceptives

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

Table 2: Drugs Which May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
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 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.
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.

Table 2: Drugs Which May Decrease the Efficacy of Oral Contraceptives

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	Analgesics Antihistamines Antimigraine preparations Phenylbutazone preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

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

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

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

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

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

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

Table 3: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde	Use with caution.
Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another non-hormonal method of contraception.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another non-hormonal method of contraception.
	Lamotrigine	Decreased lamotrigine levels, may lead to breakthrough seizures.	Use another non-hormonal method of contraception.
Antidiabetic drugs	Oral hypoglycemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another non-hormonal method of contraception. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen oral contraceptive or use another non-hormonal method of contraception.
	Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic acid		Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors.	Avoid concomitant use.

Table 3: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing oral contraceptives can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol lowering agents	Clofibrate	Their action may be antagonized by oral contraceptives. Oral contraceptives may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Direct-acting antiviral (DAA) medicinal products	Ombitasvir, Paritaprevir, 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	Concomitant administration of YAZ PLUS with DAA medicinal products (such as ombitasvir, paritaprevir, and dasabuvir) is contraindicated (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)
Folic acid		Oral contraceptives have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose oral contraceptives. If galactorrhea or hyperprolactinemia occurs, use other non-hormonal method of contraception.
Sedatives and hypnotics	Chlordiazepoxide Diazepam Lorazepam Oxazepam	Increased effect (increased metabolism).	Use with caution.

Table 3: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: eg, depression	Use with caution.
Vitamin B ₁₂		Oral contraceptives have been reported to reduce serum levels of Vitamin B ₁₂	May need to increase dietary intake, or supplement.

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

Concomitant administration of levomefolate calcium did not affect the rate and extent of absorption of drospirenone and ethinyl estradiol.

No formal drug-drug interaction studies have been conducted with YAZ PLUS tablets.

Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, eg, antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate levels and decrease the efficacy of folates by inhibition of the human dihydrofolate reductase (eg, methotrexate, trimethoprim, sulfasalazine, and triamteren) or by reducing folate absorption (eg, cholestyramine), or via unknown mechanisms (eg, antiepileptics such as carbamazepine, phenytoin, phenobarbital and primidone and valproic acid).

Interactions With Drugs That Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking YAZ PLUS with other drugs (see **WARNINGS AND PRECAUTIONS**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the YAZ[®] clinical trials.

A drug-drug interaction study of DRSP 3 mg/estradiol 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/estradiol treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on day 14. On day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/estradiol group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

Drug-Food Interactions

The effect of food on absorption of drospirenone, ethinyl estradiol and levomefolate calcium following administration of YAZ PLUS has not been established (see **ACTION AND CLINICAL PHARMACOLOGY - Effect of Food** for more details).

Drug-Herb Interactions

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

Drug-Laboratory Test Interactions

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

A. *Liver Function Tests*

Aspartate serum transaminase (AST) - variously reported elevations
Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated

B. *Coagulation Tests*

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

C. *Thyroid Function Tests*

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T₃ resin uptake.

D. *Lipoproteins*

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

E. *Gonadotropins*

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

F. *Glucose Tolerance*

Oral glucose tolerance remained unchanged or was slightly decreased.

G. *Vitamin B12*

Folates may mask vitamin B₁₂ deficiency.

Tissue Specimens

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

Drug-Lifestyle Interactions

No studies on the effects of YAZ PLUS on the ability to drive or use machines have been performed.

Metabolic Interactions

Drospirenone

Metabolism of drospirenone (DRSP) and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in in vitro and in vivo studies (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics: *Metabolism***). In in vitro studies, DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 and CYP3A4 activity was investigated in clinical pharmacokinetic studies using omeprazole, simvastatin and midazolam as marker substrates. In 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 levels, 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.

4.6 Fertility, Pregnancy and Lactation

Pregnant Women

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with YAZ PLUS, further intake must be stopped and a prenatal vitamin containing folate supplementation should be initiated. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child. One infant was born with esophageal atresia during treatment with YAZ PLUS[®], a COC of similar composition (ethinyl estradiol and drospirenone only) but with different dose and regimen. The causal association is unknown.

Nursing Women

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

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

Fertility

Temporary infertility may occur occasionally after discontinuation of treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects of YAZ PLUS on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

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

- arterial and venous thromboembolism
- being diagnosed with breast cancer
- benign and malignant hepatic tumors
- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension
- mesenteric thrombosis
- myocardial infarction
- neuro-ocular lesions (eg, retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

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

- abdominal pain
- amenorrhea during and after treatment
- angioedema (exogenous estrogens may induce or exacerbate symptoms of angioedema in women with hereditary angioedema)
- auditory disturbances
- breakthrough bleeding
- breast changes (tenderness, enlargement and secretion)
- cataracts
- changes in appetite
- change in corneal curvature (steepening)
- changes in libido

- change in menstrual flow
- change in weight (increase or decrease)
- changes in glucose tolerance or effect on peripheral insulin resistance
- chloasma or melasma which may persist
- cholestatic jaundice
- chorea
- Crohn's disease
- cystitis-like syndrome
- mental depression
- diarrhea
- dizziness
- dysmenorrhea
- edema
- endocervical hyperplasia
- erythema multiforme
- erythema nodosum
- gallstone formation^a
- gastrointestinal symptoms (such as abdominal cramps and bloating)
- headache
- hemolytic uremic syndrome^a
- hemorrhagic eruption
- herpes gestationis^a
- hirsutism
- hypersensitivity
- hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- hypertension
- impaired renal function
- increase in size of uterine leiomyomata
- intolerance to contact lenses
- jaundice related to cholestasis^a
- liver function disturbances
- loss of scalp hair
- migraine
- nervousness
- optic neuritis
- otosclerosis-related hearing loss^a
- pancreatitis
- porphyria
- possible diminution in lactation when given immediately postpartum
- premenstrual-like syndrome
- pruritus related to cholestasis^a
- rash (allergic)
- Raynaud's phenomenon
- reduced tolerance to carbohydrates
- retinal thrombosis
- rhinitis

- spotting
- Sydenham’s chorea^a
- systemic lupus erythematosus^a
- temporary infertility after discontinuation of treatment
- urticaria
- ulcerative colitis
- vaginal candidiasis
- vaginal discharge
- vaginitis

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The clinical development programs were conducted independently for each of the 3 indications and utilized indication-specific inclusion criteria, study designs, and settings. Thus, the safety results of the studies are presented separately and are not pooled.

For the indications of conception control and treatment of moderate acne vulgaris in women \geq 14 years of age, the clinical trials were conducted with YAZ[®] (3.0 mg drospirenone, 0.020 mg ethinyl estradiol). For the indication of improvement in folate status in women who choose to use oral contraception, the clinical studies were conducted with YAZ PLUS (3.0 mg drospirenone, 0.020 mg ethinyl estradiol, 0.451 mg levomefolate calcium tablets and 0.451 mg levomefolate calcium tablets).

The following adverse drug reactions were reported at a frequency \geq 1% (**common**) in pivotal clinical trials using YAZ[®] (3.0 mg drospirenone, 0.020 mg ethinyl estradiol) as an oral contraceptive:

Table 4: Adverse Drug Reactions With Frequency of \geq 1% (*common*) in Pivotal OC Clinical Trials With YAZ^{®a} (N=2438)

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

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

a YAZ[®] contains 3.0 mg drospirenone and 0.020 mg ethinyl estradiol

The following adverse drug reactions were reported at a frequency $\geq 1\%$ (**common**) in pivotal clinical trials using YAZ[®] (3.0 mg drospirenone, 0.020 mg ethinyl estradiol) in the treatment of moderate acne vulgaris:

Table 5: Adverse Drug Reactions With Frequency of $\geq 1\%$ (common**) in Pivotal Moderate Acne Vulgaris Clinical Trials With YAZ^{®a} (N=536)**

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

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

a YAZ[®] contains 3.0 mg drospirenone and 0.020 mg ethinyl estradiol

The following adverse drug reactions were reported at a frequency $\geq 1\%$ (**common**) in the pivotal clinical trial using YAZ PLUS (3.0 mg drospirenone, 0.020 mg ethinyl estradiol, 0.451 mg levomefolate calcium tablets and 0.451 mg levomefolate calcium tablets) for the improvement in folate status:

Table 6: Adverse Drug Reactions With Frequency of $\geq 1\%$ (common**) in the Pivotal Folate Supplementation Clinical Trial With YAZ PLUS^a (N=285)**

MedDRA System Organ Class	MedDRA Term	n	%
Psychiatric disorders	Libido decreased	4	1.4
Nervous system disorders	Headache	5	1.8
Investigations	Low density lipoprotein increased	3	1.1

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = total number, n = number of subjects

a YAZ PLUS contains 3.0 mg drospirenone, 0.020 mg ethinyl estradiol, 0.451 mg levomefolate calcium and 0.451 mg levomefolate calcium

Note: The most appropriate MedDRA term (version 14.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

Less Common Clinical Trial Adverse Drug Reactions

The following adverse drug reactions were seen at a frequency of $< 1\%$ and $\geq 0.1\%$ (**uncommon**) in pivotal-clinical trials using YAZ[®] (3.0 mg drospirenone, 0.020 mg ethinyl estradiol) as an oral contraceptive:

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

Cardiovascular system: hypertension, migraine, varicose vein

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

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

Musculoskeletal system: muscle cramps

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

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

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

The following adverse drug reactions were seen at a frequency of <1% and \geq 0.1% (**uncommon**) in pivotal clinical trials using YAZ[®] (3.0 mg drospirenone, 0.020 mg ethinyl estradiol) in the treatment of moderate acne vulgaris:

Body as a whole: abdominal pain, asthenia, malaise

Cardiovascular system: hypertension, migraine

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

The following adverse drug reactions were seen at a frequency of <0.1% and \geq 0.01% (**rare**) in pivotal clinical trials using YAZ[®] (3.0 mg drospirenone, 0.020 mg ethinyl estradiol) as an oral contraceptive:

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

Cardiovascular system: phlebitis, syncope, tachycardia, vascular disorder

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

Endocrine system: endocrine disorder

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

Nervous system: hot flashes, insomnia, vertigo

Respiratory system: epistaxis

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

Special senses: conjunctivitis, dry eye, eye disorder

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

The following adverse drug reactions were seen at a frequency of <1% and \geq 0.1% in the pivotal clinical trial using YAZ PLUS for the improvement in folate status:

Gastrointestinal disorders: abdominal distension, nausea

General disorders and administration site conditions: irritability

Infections and Infestations: fungal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection

Investigations: gamma-glutamyltransferase increased, smear cervix abnormal, weight increased

Musculoskeletal and connective tissue disorders: pain in extremity

Neoplasms benign, malignant and unspecified: cervix carcinoma stage 0

Nervous: dizziness, migraine

Psychiatric disorders: affect lability, depressed mood, mood altered

Reproductive system and breast disorders: breast cyst, breast mass, breast tenderness, cervical dysplasia, dysmenorrhea, genital hemorrhage, genital rash, menorrhagia, menstrual disorder, vulvovaginal discomfort

Skin and subcutaneous tissue disorders: acne, alopecia

Postmarket Adverse Drug Reactions

The following unexpected adverse events have also been reported very rarely in users of YAZ[®], (3.0 mg drospirenone, 0.020 mg ethinyl estradiol) but a causal relationship has not been established: hot/cold sensations, muscle spasms, muscle twitching, and erythema multiforme.

In addition, venous and arterial thromboembolic events (peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction and stroke not specified as hemorrhagic) have been identified as Adverse Drug Reactions (ADRs) from postmarketing experience reported in association with the use of YAZ (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Hematologic**). Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

To report any side effect(s):

National Pharmacovigilance and Drug Safety Center (NPC).

Fax: + 966 - 11 - 205 - 7662.

Call NPC at +966 - 11 - 2038222,

Ext.: 2317 - 2356 - 2353 - 2354 - 2334 - 2340.

Toll - free: 8002490000.

E - mail: npc.drug@sfd.gov.sa.

Website: www.sfd.gov.sa/npc

4.9 Overdose

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

There have been no reports of overdose with YAZ PLUS (drospirenone, ethinyl estradiol, levomefolate calcium tablets and levomefolate calcium 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.

Folates may mask vitamin B₁₂ deficiency.

Levomefolate calcium doses of 17 mg/day (37-fold higher than the levomefolate calcium dose of YAZ PLUS) were well tolerated after long-term treatment up to 12 weeks.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Oral Contraceptives

ATC Code

G03AA12

Mechanism of Action

YAZ PLUS is a combination oral contraceptive consisting of 28 film-coated tablets of which 24 tablets each contain the progestin drospirenone (3.0 mg), a low dose of the estrogen ethinyl estradiol (0.020 mg) and the vitamin levomefolate calcium (0.451 mg) and 4 tablets each contain the vitamin levomefolate calcium (0.451 mg). 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 antiglyucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

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

Levomefolate calcium is a stable salt of the naturally occurring form of folate and is the predominant folate form in foods whereas folic acid does not occur naturally. Levomefolate calcium is a metabolite of vitamin B₉. Folate deficiency is correlated with an increased risk for neural tube defects (NTDs) in the newborn, although there may also be other causes of NTDs and the use of YAZ PLUS cannot exclude their occurrence. Prevention of folate deficiency is recommended even before the onset of pregnancy in order to achieve an adequate folate status early in pregnancy. The critical time for NTDs is early in pregnancy (the closure of the neural tube is normally completed within 28 days after conception, and achievement of an adequate level of folate takes several weeks).

Pharmacodynamic effects

Drospirenone inhibits ovulation and follicular development at an oral threshold dose of 2 mg. Drospirenone 3 mg in combination with ethinyl estradiol was found to be optimal for inhibition of ovulation and cycle control. Administration of 3 extra days of hormone (24-day active containing 3.0 mg drospirenone/0.020 mg ethinyl estradiol versus a 21-day active containing 3.0 mg drospirenone/0.030 mg ethinyl estradiol) results in additional suppression of the ovary and of follicular development. This was observed in a study comparing YAZ® (3.0 mg drospirenone/0.020 mg ethinyl estradiol) with a combination oral contraceptive containing 3.0 mg drospirenone/0.030 mg ethinyl estradiol (YASMIN®) in a 21-day regimen. Hormone-containing pills of each regimen were intentionally missed on the first 3 days of the cycle and subsequent follicular development was monitored.

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

Drospirenone (2, 3, or 4 mg) in combination with ethinyl estradiol (0.020 mg) displayed a favourable effect on the lipid profile with an increase in HDL and a slight decrease in LDL. Total cholesterol remained unchanged. In addition, oral glucose tolerance was slightly increased, but remained within the reference range.

Drospirenone had no effect on the biosynthesis of SHBG, and when administered in conjunction with ethinyl estradiol (0.020 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).

The pharmacodynamic study evaluated the impact of YAZ PLUS on plasma folate and red blood cell (RBC) folate levels. A randomized, double-blind, active controlled, parallel group study compared plasma folate and RBC folate levels during a 24-week treatment period with YAZ PLUS as compared to YAZ® (3.0 mg drospirenone/0.020 mg ethinyl estradiol) alone in a population with mandatory folate fortification in staple food.

Clinical Efficacy and Safety

Contraception

General Information

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

Table 7: Reported Pregnancies per 100 Women per Year

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

Study Demographics and Trial Design

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

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

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

Table 8: Overview of Studies Evaluating the Efficacy of YAZ® for Conception Control

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

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

a Full analysis set (FAS)

b Not available in Canada

Study Results

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

The adjusted Pearl Index (PI_c) in the YAZ[®] studies was calculated on the basis of 7 pregnancies rated as method failure (5 in Study 303740 and 2 in Study 308021) and a treatment exposure of 581,408 days (corresponding to 1,597.2 wy). The PI was calculated to be 0.44 with an upper 2-sided 95% confidence limit of 0.90 (see Table 9). The individual study PI_c and upper 2-sided 95% confidence limit values were 0.72 and 1.69 for Study 303740, and 0.22 and 0.80 for Study 308021, respectively.

Table 9: Pearl Index (PI) and Adjusted Pearl Index (PI_c) – Data of Studies 303740 and 308021

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

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

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

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

In addition to the calculation of the PI, a life table analysis was performed for the time to the occurrence of a pregnancy in the two 13-cycle pivotal studies. The cumulative failure rate, ie, the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of unintended pregnancies considered to have occurred “during treatment.”

The pooled Kaplan-Meier estimation after the last conception date after up to 1 year of treatment was 0.0085 with a 95% CI of 0.0052 to 0.0138, ie, the probability of contraceptive protection was estimated to be 0.9915 (99.15%). The estimation of the 1-year pregnancy rate for Study 303740 was 1.26% with a 95% CI of 0.0052 to 0.0201, and for Study 308021 this was 0.5% with a 95% CI of 0.0021 to 0.0119.

Bleeding Pattern

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

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

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

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

An overview of the bleeding pattern parameters for both treatment groups in Study 308020 is presented in Table 10 for Reference Period 1 and Reference Period 2. The mean values for all the parameters studied were very similar in both treatment groups.

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

Table 10: Bleeding Pattern Parameters in Reference Period 1 and Reference Period 2 – FAS (Study 308020)

	n	Mean	SD
Reference Period 1			
YAZ			
Number of bleeding/spotting days	196	23.6	10.1
Number of bleeding/spotting episodes	196	4.4	1.0
Mean length of bleeding/spotting episodes (days)	196	5.6	3.3
Maximum length of bleeding/spotting episodes (days)	196	8.8	6.8
Number of spotting only days	196	9.5	7.1
Number of spotting only episodes	196	0.6	0.9
Mean length of spotting only episodes (days)	78 ^a	2.6	1.6
Maximum length of spotting only episodes (days)	78 ^a	3.0	2.4
Comparator ^b			
Number of bleeding/spotting days	165	24.0	8.5
Number of bleeding/spotting episodes	165	4.3	0.9
Mean length of bleeding/spotting episodes (days)	165	5.7	2.3
Maximum length of bleeding/spotting episodes (days)	165	8.6	5.5
Number of spotting only days	165	8.9	7.1
Number of spotting only episodes	165	0.5	0.8
Mean length of spotting only episodes (days)	54 ^a	2.8	2.6
Maximum length of spotting only episodes (days)	54 ^a	3.0	2.7
Reference Period 2			
YAZ			
Number of bleeding/spotting days	182	16.1	6.4
Number of bleeding/spotting episodes	182	3.4	1.1
Mean length of bleeding/spotting episodes (days)	180	4.8	1.5
Maximum length of bleeding/spotting episodes (days)	180	6.0	2.6
Number of spotting only days	182	6.2	4.8
Number of spotting only episodes	182	0.5	0.9
Mean length of spotting only episodes (days)	48 ^a	3.0	2.2
Maximum length of spotting only episodes (days)	48 ^a	3.6	2.8
Comparator ^b			
Number of bleeding/spotting days	153	16.6	8.5
Number of bleeding/spotting episodes	153	3.3	0.9
Mean length of bleeding/spotting episodes (days)	153	5.1	2.3
Maximum length of bleeding/spotting episodes (days)	153	6.3	5.5
Number of spotting only days	153	5.6	7.1
Number of spotting only episodes	153	0.3	0.8
Mean length of spotting only episodes (days)	32 ^a	3.1	2.6
Maximum length of spotting only episodes (days)	32 ^a	3.6	2.7

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

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

b Not available in Canada

Bleeding pattern parameters for Study 303740 for Reference Periods 1 to 4 are presented in Table 11.

Table 11: Bleeding Pattern Parameters by Reference Period – YAZ® Treatment Group - FAS (Study 303740)

	n	Mean	SD
Reference Period 1			
Number of bleeding/spotting days	890	22.49	10.34
Number of bleeding/spotting episodes	890	4.28	1.14
Mean length of bleeding/spotting episodes (days)	889	5.43	2.74
Max. length of bleeding/spotting episodes (days)	889	8.45	5.96
Number of spotting only days	890	7.72	7.67
Number of spotting only episodes	890	0.63	1.01
Mean length of spotting only episodes (days)	340	3.22	2.40
Maximum length of spotting only episodes (days)	340	3.80	3.02
Reference Period 2			
Number of bleeding/spotting days	853	15.09	7.36
Number of bleeding/spotting episodes	853	3.25	1.09
Mean length of bleeding/spotting episodes (days)	837	4.71	1.94
Max. length of bleeding/spotting episodes (days)	837	6.18	3.42
Number of spotting only days	853	5.16	5.31
Number of spotting only episodes	853	0.56	1.02
Mean length of spotting only episodes (days)	285	2.85	2.00
Maximum length of spotting only episodes (days)	287	3.20	2.25
Reference Period 3			
Number of bleeding/spotting days	792	14.48	6.98
Number of bleeding/spotting episodes	792	3.18	1.00
Mean length of bleeding/spotting episodes (days)	774	4.54	1.79
Max. length of bleeding/spotting episodes (days)	774	5.87	3.24
Number of spotting only days	792	5.04	5.64
Number of spotting only episodes	792	0.52	0.99
Mean length of spotting only episodes (days)	234	2.93	1.79
Maximum length of spotting only episodes (days)	236	3.42	2.45
Reference Period 4			
Number of bleeding/spotting days	719	14.56	7.23
Number of bleeding/spotting episodes	719	3.20	1.04
Mean length of bleeding/spotting episodes (days)	706	4.57	1.93
Max. length of bleeding/spotting episodes (days)	706	5.74	3.38
Number of spotting only days	719	5.16	5.82
Number of spotting only episodes	719	0.56	1.00
Mean length of spotting only episodes (days)	215	2.89	1.63
Maximum length of spotting only episodes (days)	234	3.25	2.23

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

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

The results were similar for the PPS.

Cycle Control

A summary of withdrawal and intracyclic bleeding data is presented in Table 12 for the 3 pivotal studies, based on the FAS population.

Table 12: Frequency of Withdrawal and Intracyclic Bleeding – FAS

Cycle	Parameter No. of Women With:	Study							
		303740		308020			301888		
		YAZ [®] (EE/DRSP) n/N (%)	YAZ [®] (EE/DRSP) n/N (%)	Comparator (EE/DSG) ^a n/N (%)		YAZ [®] (EE/DRSP) n/N (%)	Comparator (EE/DSG) ^a n/N (%)		
1	WB	838/935 (89.6)	178/207 (86.0)	148/170 (87.1)	27/29 (93.1)	22/29 (75.9)			
	IB	231/935 (24.7)	200/207 (96.6)	165/170 (97.1)	7/29 (24.1)	7/29 (24.1)			
3	WB	821/874 (93.9)	187/196 (95.4)	156/166 (94.0)	26/27 (96.3)	27/28 (96.4)			
	IB	121/874 (13.8)	34/196 (17.3)	27 (16.3)	7/27 (25.9)	4/28 (14.3)			
6	WB	773/843 (91.7)	171/182 (94.0)	149/153 (97.4)	24/26 (92.3)	25/25 (100)			
	IB	116/843 (13.8)	16/182 (8.8)	17/153 (11.1)	5/26 (19.2)	3/25 (12.0)			
9	WB	709/763 (92.9)	-	-	-	-			
	IB	76/763 (10.0)	-	-	-	-			
13	WB	482/523 (92.2)	-	-	-	-			
	IB	81/523 (15.5)	-	-	-	-			

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

a Not available in Canada

Withdrawal Bleeding

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

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

Intracyclic Bleeding

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

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

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

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

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

The results were similar for the PPS.

Acne Therapy

Study Demographics and Trial Design

The efficacy of YAZ[®] (EE/DRSP) in treating moderate acne vulgaris was evaluated in 2 pivotal, multicentre, double-blind, randomized clinical trials carried out in North America. An overview of the 2 studies is presented below in Table 13:

Table 13: Overview of Studies Evaluating the Efficacy of YAZ[®] in the Treatment of Moderate Acne Vulgaris

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

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

a Amended full analysis set (Amended FAS)

b Full analysis set (FAS)

In the early course of the studies, the original diagnosis, “mild to moderate acne vulgaris”, was amended to “moderate acne vulgaris.” The amended FAS was considered the primary efficacy analysis. Table 14 provides an overview of the primary efficacy variable results based on the amended FAS. YAZ[®] produced clinically and statistically significant anti-acne effects in all primary efficacy variables. These results are presented in detail below.

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

Study Results

Study 306820

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

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

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

Study 306996

A total of 538 women (270 in the YAZ[®] group and 268 in the placebo group) were randomized and dispensed study medication. After 6 treatment cycles, the reduction from baseline to endpoint in mean percentage inflammatory lesion count was 50.9% for YAZ[®] versus 34.7% for placebo. The adjusted mean difference was -15.752% ($P < 0.0001$ for YAZ[®] versus placebo). The reduction from baseline to endpoint in mean percentage noninflammatory lesion count was 42.8% for YAZ[®] versus 26.3% for placebo. The adjusted mean difference was -16.010% ($P < 0.0001$ for YAZ[®] versus placebo). The reduction from baseline to endpoint in mean percentage total lesion count was 46.5% for YAZ[®] versus 30.9% for placebo. The adjusted mean difference was -15.194% ($P < 0.0001$ for YAZ[®] versus placebo). The reductions in inflammatory lesion count, noninflammatory lesion count, and total lesion count over time (from baseline to each visit) were statistically significant within both the YAZ[®] and placebo groups.

For the investigator’s global assessment, improvement of facial acne (eg, subjects rated as “clear” or “almost clear”) was observed in subjects treated with YAZ[®] (21.2%) and placebo (9.3%). The resulting odds ratio was 2.921 (CI: 1.598, 5.341; $P = 0.0004$).

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

Table 14: Overview of Primary Efficacy Variable Results - Amended FAS (Pooled Data of Studies 306820 and 306996)

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

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

a Difference in adjusted treatment means (ie, YAZ[®] minus placebo)

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

Folate Supplementation

Study Demographics and Trial Design

The clinical development program for YAZ PLUS for the improvement of folate status in women who elect to use oral contraception consisted of a clinical trial carried out in the United States (US). An overview of the study is presented below in Table 15.

Table 15: Overview of the Study Evaluating the Efficacy of YAZ PLUS for the Improvement in Folate Status

Study	Study Objective/ Design	Route of Administration/ Duration	Study Drug	No. of Subjects ^a	Mean Age (Range) [Years]	Mean BMI [kg/m ²]
310662	Efficacy/Safety Multicentre, randomized, double-blind, active-control, parallel group study	Oral/ One medicated tablet daily for 24 weeks	Test product: YAZ PLUS (DRSP 3 mg + EE 0.02 mg + 0.451 mg levomefolate calcium and 0.451 mg levomefolate calcium)	285	24.8 (18-40)	24.1 ± 3.9
			Comparator: YAZ [®] (DRSP 3 mg + EE 0.02 mg)	94	24.6 (18-39)	24.0 ± 3.6

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

a Full analysis set (FAS)

Study Results

Study 310662

Study 310662 was a multicenter, randomized, double-blind, active-controlled, parallel group study conducted in the United States (US). Plasma folate and red blood cell (RBC) folate levels were investigated during a 24-week treatment period with YAZ PLUS as compared to YAZ alone in a US population with folate fortified food. A total of 379 healthy women between 18 and 40 years of age with no restrictions on folate supplementation received YAZ PLUS (n=285) or YAZ (n=94). The plasma and RBC folate levels at Week 24 were the co-primary endpoints. Figure 1 and Figure 2 display the results for plasma and RBC folate, respectively, among evaluable subjects in each arm of the study.

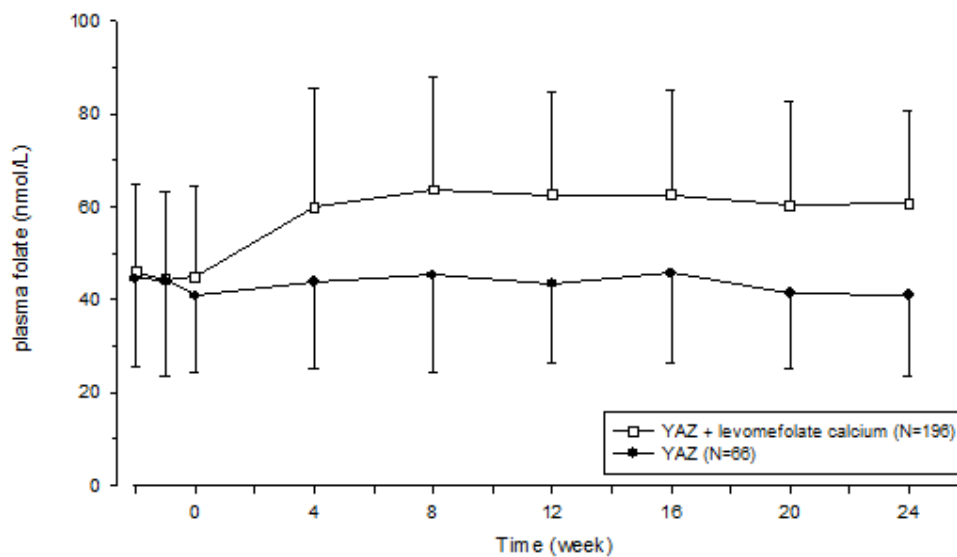


Figure 1: Study 310662 – Mean concentration-time curves (and SD) of plasma folate after daily oral administration of YAZ PLUS and YAZ®

Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations (SD) which are shown in only one direction to improve readability. Data are based on per protocol analysis populations.

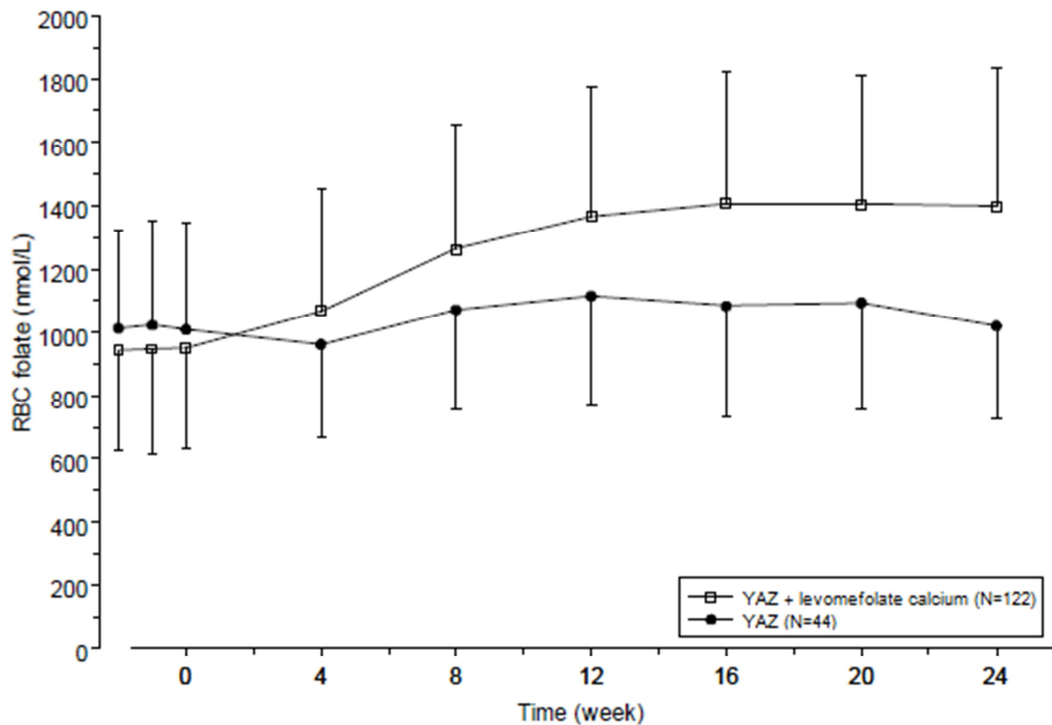


Figure 2: Study 310662 - Mean concentration-time curves (and SD) of RBC folate after daily oral administration of YAZ PLUS and YAZ®

Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations (SD) which are shown in only one direction to improve readability. Data are based on per protocol analysis populations and calculated according to scenario B.

The potential to reduce the incidence of neural tube defects (NTDs) with folate supplementation is well established based on a body of evidence derived from randomized, controlled trials, non-randomized intervention trials, and observational studies using folic acid. Therefore, Health Canada Prenatal Nutrition Guidelines for Health Professionals and the Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guidelines recommend that women of childbearing age consume supplemental folic acid in a minimum dose of 0.4 mg (400 µg) daily.

5.2 Pharmacokinetic properties

Table 16: Summary of Pharmacokinetic Parameters of Drospirenone, Ethinyl Estradiol and L-5-methyl-THF after single oral administration of the hormone containing YAZ PLUS tablet (3 mg DRSP, 0.02 mg EE and 0.451 mg levomefolate calcium) in Healthy Young Women

Treatment	Baseline	N	C _{max} pg/mL	AUC(0-t _{last}) (pg·h/mL)	AUC (pg·h /mL)	t _{max} (h)	t _{1/2} (h)
EE	n/a	39	41.9 (34.4%)	370 (34.4%)	424 (38.7%) (N=8)	1.52 (1.0- 4.18)	9.91 (35.1%) (N=8)
			(ng/mL)	(ng·h/mL)			
DRSP	n/a	36	26.7 (25.9%)	383 (30.7%)	418 (31.3%) (N=33)	2.0 (0.5-4.1)	29.7 (30.4%) (N=33)
			(nmol/L)	(nmol·h/L)		(h)	
L-5-methyl- THF	un- corrected	40	57.9 (30.4%)	370 (34.4%)	-	0.5 (0.0-4.0)	-
L-5-methyl- THF	corrected	39	44.3 (32.7%)	214 (28.7%)	-	0.5 (0.5-4.0)	-

Abbreviations: AUC = area under the curve, C_{max} = maximum concentration, h = hour, mL = milliliter, L = liter, N = number of subjects, n/a = not applicable, ng – nanogram, pg = picogram, t_{1/2} = elimination half life, t_{max} = time of maximum concentration

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

Table 17: Summary of Pharmacokinetic Parameters of L-5-methyl-THF after single oral administration of the hormone free YAZ PLUS tablet (0.451 mg levomefolate calcium) in Healthy Young Women

Treatment	Baseline	N	C _{max} (nmol/L)	AUC(0-t _{last}) (nmol·h/L)	t _{max} (h)
L-5-methyl- THF	un- corrected	40	57.7 (35.5%)	370 (33.6%)	0.5 (0.5-2.0)
L-5-methyl- THF	corrected	40	44.2 (39.4%)	217 (28.1%)	0.5 (0.5-2.0)

Abbreviations: AUC = area under the curve, C_{max} = maximum concentration, h = hour, L = liter, N = number of subjects, t_{max} = time of maximum concentration

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

YAZ PLUS and YAZ[®] have been shown to be equivalent with respect to DRSP and EE.

Absorption

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of YAZ PLUS which is a combination tablet of drospirenone, ethinyl estradiol stabilized by betadex as a clathrate (molecular inclusion complex) and levomefolate calcium has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1 to 2 hours after administration of YAZ PLUS.

After single oral administration of YAZ PLUS, the mean maximum concentration of EE was 41.9 pg/mL and was reached 1.52 hours after administration. For DRSP, the mean maximum concentration was 26.7 ng/mL and was reached 2.0 hours after administration (see Table 16 above).

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of YAZ (3.0 mg drospirenone, 0.020 mg ethinyl estradiol), steady-state DRSP concentrations were observed after 8 days. There was about 2- to 3-fold accumulation in serum C_{max} and $AUC_{(0-24h)}$ values of DRSP following multiple-dose administration of YAZ (3.0 mg drospirenone, 0.020 mg ethinyl estradiol).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of YAZ (3.0 mg drospirenone, 0.020 mg ethinyl estradiol), serum C_{max} and $AUC_{(0-24h)}$ values of EE accumulate by a factor of about 1.5 to 2.0.

Levomefolate calcium is structurally identical to L-5-methyltetrahydrofolate (L-5-methyl-THF), the predominant folate form in food. Mean baseline concentrations of about 15 nmol/L are reached in populations without folate food fortification under normal nutritional conditions. Orally administered levomefolate calcium is absorbed rapidly and is incorporated into the body folate pool. Peak plasma concentrations of about 45 nmol/L above baseline are reached within approximately 0.5 hours after single oral administration of 0.451 mg levomefolate calcium given either alone (see Table 17 above) or in combination with EE/DRSP (see Table 16 above).

Steady-state conditions for L-5-methyl-THF in plasma after intake of 0.451 mg levomefolate calcium are reached after about 8-16 weeks depending on the baseline levels. In red blood cells achievement of steady state is delayed due to the long life-span of red blood cells of about 120 days.

Effect of Food

The rate of absorption of DRSP and EE following single administration of 2 tablets, each containing 3 mg DRSP and 0.030 mg EE was slower under fed conditions, with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast the extent of absorption of EE was reduced by about 20% under fed conditions.

The effect of food on absorption of levomefolate calcium following administration of YAZ PLUS has not been evaluated.

Distribution

DRSP and EE serum levels decline in 2 phases. The apparent volume of distribution of DRSP is approximately 4 L/kg, and that of EE is reported to be approximately 4 to 5 L/kg.

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

Biphasic kinetics is reported for folates with a fast- and a slow-turnover pool. The fast-turnover pool probably reflecting newly absorbed folate is consistent with the terminal half-life of approximately 4 - 5 hours after single oral administration of 0.451 mg levomefolate calcium. The slow-turnover pool reflecting turnover of folate polyglutamate has a mean residence time of greater than or equal to 100 days. Exogenous folate and an enterohepatic folate cycle help to maintain a constant supply of L-5-methyl-THF.

Metabolism

The 2 main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP, generated by opening of the lactone ring, and the 4,5-dihydrodrospirenone-3-sulfate, formed by reduction and subsequent sulfation. These metabolites were shown not to be pharmacologically active. DRSP is also subject to oxidative metabolism catalyzed by CYP3A4.

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

L-5-methyl-THF is the predominant folate transport form in blood under physiological conditions and during folic acid and levomefolate calcium administration.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single- and multiple-dose regimens. Excretion of DRSP was nearly complete after 10 days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38% to 47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17% to 20% of the metabolites were excreted as glucuronides and sulfates.

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

L-5-methyl-THF is eliminated from the body by urinary excretion of intact folates and catabolic products as well as fecal excretion through a biphasic kinetics process.

Characteristics in patients

Pediatrics

The safety and efficacy of YAZ PLUS has been established in women aged 18 and over. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated. The maximum recommended daily dose for folate supplementation in adolescents is less than that for adults (see **DOSAGE AND ADMINISTRATION. - Special Notes on Administration, Folate Supplementation**).

Geriatrics

YAZ PLUS is not indicated for use in postmenopausal women.

Race

No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (aged 20-35 years) when 3.0 mg DRSP/0.020 mg EE was administered daily for 21 days. The effect of race on the disposition of YAZ PLUS has not been evaluated.

Hepatic Insufficiency

YAZ PLUS is contraindicated in patients with hepatic dysfunction (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). The mean exposure to DRSP in women with moderate hepatic impairment is approximately 3 times higher than the exposure in women with normal hepatic function. The mean terminal half-life of DRSP for women with moderate hepatic impairment was 1.8 times greater than for women with normal hepatic function. YAZ PLUS has not been studied in women with severe hepatic impairment.

Renal Insufficiency

YAZ PLUS is contraindicated in patients with renal insufficiency (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30-65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium-sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those in the group with normal renal function (CLcr, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLcr, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in 5 of the 7 subjects who continued use of potassium-sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range and who are concomitantly using potassium sparing drugs.

5.3 Preclinical Data

Animal Pharmacology

Drospirenone

Drospirenone exhibits potent progestational activity in a variety of animal models. In ovariectomized pregnant rats treated with drospirenone 3 mg/day sc in combination with ethinyl estradiol 0.1 µg/day sc, maintenance of pregnancy was comparable to intact control animals. Drospirenone effectively inhibited ovulation in mice and rats with half-maximal effects observed at subcutaneous doses of approximately 0.1 and 1 mg/day, respectively, and an oral dose of 1 mg/day (rats). Following subcutaneous administration of drospirenone, a marked transformation of the endometrium was detected in castrated, infantile female rabbits, with a threshold dose of 100 to 300 µg/day. In vitro, drospirenone bound with high affinity to the progesterone receptor, and the binding affinity was not affected by the presence of ethinyl estradiol.

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

Significant antimineralocorticoid activity, characterized by increased sodium excretion and an increase of the urinary Na⁺/K⁺ ratio, was observed following single oral or subcutaneous administration of drospirenone to adrenalectomized, aldosterone-substituted rats. Drospirenone was 5 to 10 times more potent than spironolactone, and its aldosterone antagonist activity was not affected by concomitant administration of ethinyl estradiol. When administered for 21 days to ovariectomized female rats, drospirenone (10 mg/day) stimulated the Na⁺/K⁺ excretion ratio over the entire treatment period, while spironolactone (10 mg/day) became ineffective after the initial treatment phase due to counter-regulation. Drospirenone also exhibited significant antimineralocorticoid activity in vitro, inhibiting aldosterone-stimulated electrogenic sodium transport 10 times more effectively than either spironolactone or progesterone. In vitro, drospirenone binds with high affinity to the mineralocorticoid receptor.

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

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

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

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

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

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

Ethinyl estradiol

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

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

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

TOXICOLOGY

Acute Toxicity

Drospirenone

Table 18 below summarizes the median lethal doses (LD₅₀) determined in acute toxicity studies with drospirenone.

Table 18: LD₅₀ Values for Drospirenone

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

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

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

Levomefolate calcium

Levomefolate calcium was evaluated for acute oral and dermal toxicity potential in male and female rats after a single administration of 2000 mg/kg. There were no remarkable clinical or necropsy findings. There were no signs of intoxication, local irritation, or evidence of organ changes at gross necropsy. In female New Zealand White rabbits, levomefolate calcium was not irritating to the skin. No potential for skin sensitization was observed in a Guinea pig maximization test.

The main impurities of levomefolate calcium were also well-tolerated and non lethal in male and female rats after a single oral administration of a limit dose of 2000 mg/kg and were not mutagenic in vitro in bacterial mutagenicity (Ames) assays.

Long-term Toxicity

The long-term toxicity of drospirenone, alone and in combination with ethinyl estradiol, was investigated after daily intra-gastric administration of the following doses.

Table 19: Long-term Toxicity Studies Conducted With Drospirenone (DRSP) and Ethinyl Estradiol (EE)

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

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

Changes observed following administration of drospirenone alone included:

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

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

Synergism of other effects was observed in mice and rats and included atrophy of ovarian interstitial glands, decreased luteal mass and sexual cycles in mice, and decreased ovarian weights and increased hepatic N-demethylase activity in rats. In comparison with administration of either substance alone, administration of the combination to rats and cynomolgus monkeys eliminated some single substance effects (alterations in hepatic cytochrome P450 content). Overt toxicity was limited to 1 possible compound-related death in cynomolgus monkeys administered the combination at a dose of 3 mg/kg drospirenone + 0.03 mg/kg ethinyl estradiol for 11 weeks.

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

Levomefolate calcium

There were no adverse clinical or pathologic findings in male and female rats given up to 400 mg/kg levomefolate calcium daily for 13 weeks.

No clinically relevant adverse effects were observed after oral administration of 5-MTHF-Ca (racemic mixture of 5-methyl tetrahydrofolate) for 26 weeks in rats up to the dose of 120 mg/kg/day or in dogs up to the dose of 180 mg/kg/day.

Carcinogenicity

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

Table 20: Carcinogenicity Studies Conducted With Drospirenone (DRSP) and Ethinyl Estradiol (EE)

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

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

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

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

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

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

Levomefolate calcium

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate calcium.

Mutagenicity

No mutagenic effect of drospirenone was demonstrated in vitro in bacterial (*Salmonella typhimurium*, *Escherichia coli*) or mammalian (human lymphocyte, Chinese hamster) cells in the presence or absence of extrinsic metabolic activation. Drospirenone did not increase the occurrence of micronucleated red blood cells in vivo following single intragastric administration of 1000 mg/kg to mice.

Drospirenone increased unscheduled DNA synthesis in primary hepatocytes of female rats in vitro in a dose-dependent manner at a concentration of 10 to 60 µg/mL. Intragastric administration of drospirenone 10 mg/kg/day to rats for 14 consecutive days generated 2 forms of DNA adducts in male and female rat livers. Low levels of 3 compound-related DNA adducts were also observed in the livers of female mice given drospirenone 10 mg/kg/day, alone or in combination with 0.1 mg/kg/day ethinyl estradiol, in the carcinogenicity study. In contrast to these findings observed in rodent livers, results from an in vitro study conducted with drospirenone 5 µg/mL in human liver slices did not indicate a DNA adduct-forming potential of drospirenone in human tissue. Given the lack of any drospirenone-related liver tumor formation in mice and rats, the biological relevance of this interaction with DNA in the rodent liver with regard to risk assessment in humans is questionable.

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

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

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

Levomefolate calcium

Levomefolate calcium was not mutagenic in bacteria or mammalian cells in vitro or in vivo in a micronucleus test in rats even after oral administration of a single dose of 2000 mg/kg.

Reproduction and Teratology

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

Table 21: Reproductive Toxicity Studies Conducted With Drospirenone (DRSP) + Ethinyl Estradiol (EE)

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

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

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

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

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

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

Maternal toxicity, embryo-fetal toxicity and teratogenicity were not observed following oral administration of 100, 300, or 1000 mg/kg/day levomefolate calcium to pregnant female rats during organogenesis (days 5 to 19 of gestation). 5-MTHF (racemic mixture of 5-methyl tetrahydrofolate) had no effects on the fertility and reproductive performance, maternal toxicity, embryo-fetal development, nor the morphological, physical or behavioral development of the offspring when given to parental rats (prior to mating until day 21 of lactation) at doses up to 360 mg/kg/day. Treatment of pregnant rats and rabbits with 5-MTHF during organogenesis at doses up to 450 mg/kg/day revealed no signs of embryo-fetal toxicity and teratogenicity. Signs of maternal toxicity based on reduced body weight gain were observed in rabbits at the 450 mg/kg/day dose. In a peri/postnatal study with 5-MTHF in rats at doses up to 360 mg/kg (treatment from day 15 of gestation to day 21 of lactation), no maternal toxicity, nor effects on the morphological, physical or behavioral development of the offspring were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients for hormone-containing tablets: cellulose microcrystalline, croscarmellose sodium, ferric oxide red, hydroxypropylcellulose 5 cP, hypromellose 5 cP, lactose monohydrate, macrogol 6000, magnesium stearate, talc, titanium dioxide, β-cyclodextrin.

Excipients for hormone-free tablets (containing folate): cellulose microcrystalline, croscarmellose sodium, ferric oxide red, ferric oxide yellow, hydroxypropylcellulose 5 cP, hypromellose 5 cP, lactose monohydrate, macrogol 6000, magnesium stearate, talc, titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years.

6.4 Special Precautions for storage

Store in original packaging below 30°C; protect from moisture and heat.

6.5 Nature and contents of the container

YAZ PLUS (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium) tablets are available in a 28-day regimen.

Each blister pack contains 24 hormone-containing, pink and 4 hormone-free light-orange, film-coated, round tablets. The 4 hormone-free tablets contain folate (levomefolate calcium).

Each hormone-containing, pink, film-coated tablet contains 3.0 mg drospirenone, 0.020 mg ethinyl estradiol stabilized by betadex as a clathrate (molecular inclusion complex) and 0.451 mg

levomefolate calcium. The hormone-containing tablet is round with convex faces, one side embossed with the letters "Z+" in a regular hexagon

6.6 Special precautions for disposal and handling

There are no special handling instructions.

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

7. MARKETING AUTHORIZATION HOLDER

Bayer AG
Kaiser-Wilhelm-Allee 1
51373 Leverkusen, Germany.

8. SAUDI FDA REGISTRATION NUMBER

121-10-16

9. REVISION DATE

03/2017