PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrYASMIN® PLUS

3.0 mg drospirenone, 0.030 mg ethinyl estradiol, 0.451 mg levomefolate calcium tablets and 0.451 mg levomefolate calcium tablets

Oral Contraceptive

Acne Therapy

Improvement in Folate Status

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Table of Contents

[Pr]YASMIN® PLUS

Drospirenone, ethinyl estradiol, levomefolate calcium tablets and levomefolate calcium tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 - Product Information Summary

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet / 3.0 mg drospirenone, 0.030 mg ethinyl estradiol and 0.451 mg levomefolate calcium	Lactose monohydrate *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*
Oral	Tablet / 0.451 mg levomefolate calcium	Lactose monohydrate *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

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

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

CONTRAINDICATIONS

YASMIN 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
- history of or actual prodromi of a thrombosis (eg, transient ischemic attack, angina pectoris)
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  - severe hypertension (persistent values of ≥160/100 mmHg)
  - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - severe dyslipoproteinemia
  - smoking, if over age 35

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including YASMIN 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.

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 preexisting migraine headache

F. Increase in epileptic seizures

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

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

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

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

YASMIN PLUS contains 3 mg of the progestogen drospirenone (DRSP) that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. YASMIN PLUS should not be used in patients with conditions that predispose to hyperkalemia (ie, 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 OC users. As breast cancer is rare in women under 40 years of age, the excess number is small in relationship to the overall risk of breast cancer. Causation with COC use is unknown.

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

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

Cervical Cancer

The most important risk factor for cervical cancer is persistent human papillomavirus infection (HPV). Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, 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 YASMIN 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, nonsmoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Hypertension

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

Endocrine and Metabolism

Diabetes

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

Lipid and Other Metabolic Effects

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

Gastrointestinal

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

Genitourinary

Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Fibroids

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

Hematologic

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

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

Two prospective cohort studies (EURAS and INAS-OC have shown that the VTE incidence rate ranges from about 7 to 10 per 10,000 woman-years in users of oral contraceptives with low-dose estrogen (<50 µg ethinyl estradiol). In comparison, the VTE incidence rate ranges from about 2 to 3 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 VTE risk in users of oral contraceptives with low-dose estrogen (<50 µg ethinyl estradiol) is about two- to three-times higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

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

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

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

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

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

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

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

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

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

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

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

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

Hepatic/Biliary/Pancreatic

In some cases of elevated liver enzymes reported during clinical trials with YASMIN, a contributory role of YASMIN could not be ruled out. YASMIN 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 oral contraceptives with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use.

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

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

Gallbladder Disease

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

Hepatic Nodules

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

Hepatitis C

YASMIN 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. YASMIN 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 (32-34).

Neurologic

Migraine and Headache

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

Ophthalmologic

Ocular Disease

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

Ocular Lesions

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

Peri-operative Considerations

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

Psychiatric

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

Renal

Fluid Retention

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

Sexual Function/Reproduction

Return to Fertility

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

Amenorrhea

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

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

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

Reduced Efficacy

The efficacy of COCs may be reduced in the event of missed tablets, gastro-intestinal disturbances, or concomitant medication (see **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 YASMIN 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, 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, 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 YASMIN 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

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

Folates may mask vitamin B_{12} deficiency.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

- arterial and venous thromboembolism
- being diagnosed with breast cancer
- benign and malignant hepatic tumors
- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension

- mesenteric thrombosis
- myocardial infarction
- neuro-ocular lesions (eg, retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

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

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

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

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.

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

The following are the most common adverse events reported with use of YASMIN® (3.0 mg drospirenone, 0.030 mg ethinyl estradiol) during clinical trials, occurring in >1% of subjects and which may or may not be drug related: headache, menstrual disorder, breast pain, abdominal pain, nausea, leukorrhea, flu syndrome, acne, vaginal moniliasis, depression, diarrhea, asthenia, dysmenorrhea, back pain, infection, pharyngitis, intermenstrual bleeding, migraine, vomiting, dizziness, nervousness, vaginitis, sinusitis, cystitis, bronchitis, gastroenteritis, allergic reaction, urinary tract infection, pruritus, emotional lability, surgery, rash, upper respiratory infection.

The following adverse drug reactions were reported at a frequency ≥ 1% in the pivotal clinical trial using YASMIN® PLUS (3.0 mg drospirenone, 0.030 mg ethinyl estradiol, 0.451 mg levomefolate calcium tablets and 0.451 mg levomefolate calcium tablets) for the improvement in folate status:

Table 2: Adverse Drug Reactions With Frequency of ≥1% in the Pivotal Folate Supplementation Clinical Trial with YASMIN PLUS[a] (N=86)

MedDRA System Organ Class	MedDRA Term	n	%
Cardiac disorders	Cardiovascular disorder	1	1.2
Gastrointestinal	Diarrhea	6	7.0
	Gastrointestinal hypomotility	1	1.2
	Nausea	5	5.8
General disorders	Fatigue	1	1.2
	Hunger	1	1.2
	Edema peripheral	1	1.2
Infections and infestations	Vaginal candidiasis	2	2.3
Investigations	Weight increased	1	1.2
Metabolism and nutrition disorders	Food craving	1	1.2
Nervous system disorders	Headache	2	2.3
	Lethargy	1	1.2
Psychiatric disorders	Mood altered	1	1.2
	Mood swings	1	1.2
Renal and urinary	Nocturia	1	1.2
Reproductive system and breast disorders	Breast discomfort	2	2.3
	Brest pain	3	3.5
	Breast swelling	1	1.2
	Dysmenorrhea	2	2.3
	Menometrorrhagia	2	2.3
	Menorrhagia	1	1.2
	Metrorrhagia	2	2.3
	Nipple pain	1	1.2
	Vaginal discharge	2	2.3

Table 2: Adverse Drug Reactions With Frequency of ≥1% in the Pivotal Folate Supplementation Clinical Trial with YASMIN PLUS[a] (N=86)

MedDRA System Organ Class	MedDRA Term	n	%
Skin and subcutaneous	Alopecia	1	1.2
	Dermatitis acneiform	1	1.2
	Onychoclasis	1	1.2
	Rash	1	1.2
	Skin disorder	1	1.2

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

a YASMIN® contains 3.0 mg drospirenone and 0.030 mg ethinyl estradiol

Less Common Clinical Trial Adverse Drug Reactions

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

Post-Market Adverse Drug Reactions

Cumulative postmarketing experience with YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol) indicates a spontaneous reporting rate of venous thromboembolism of 5.1 events per 100 000 woman-years. (35)

The following serious and unexpected adverse reactions have also been reported very rarely in users of YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol), but a causal relationship has not been established: pancytopenia, thrombocytopenia, arrhythmia, palpitations, tachycardia, ventricular extrasystoles, sudden hearing loss, ocular hypertension, visual disturbance, vitreous opacities, ischaemic colitis, hepatitis, hyperbilirubinemia, abnormal liver function test, decreased blood sodium, bone pain, pain in extremity, fibroadenoma of breast, seizure, dysarthria, facial paresis, hemiparesis, hypoesthesia, syncope, anxiety, nervousness, panic reaction, breast cyst, hematometra due to cervical polyp, asthma, leukocytoclastic vasculitis, lichen planus, and petechiae.

Cases of erythema nodosum, erythema multiforme, and hypersensitivity (including symptoms such as rash, urticaria) have been reported as adverse drug reactions from postmarket reporting in association with the use of YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol).

In addition, venous and arterial thromboembolic events (peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction and stroke not specified as hemorrhagic) have been identified as ADRs from postmarketing experience reported in association with the use of YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol) (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Hematologic**). Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following unexpected adverse events have also been reported very rarely in users of YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol); but a causal relationship has not been established: hot/cold sensations, muscle spasms, and muscle twitching.

Single cases of celiac disease, dermoid cyst, exostosis have been reported as serious and unexpected adverse drug reactions from postmarket reporting in association with the use of YASMIN PLUS (3.0 mg drospirenone, 0.030 mg ethinyl estradiol, 0.451 mg levomefolate calcium tablets and 0.451 mg levomefolate calcium tablets).

The following unexpected adverse events have also been reported very rarely in users of YASMIN PLUS (3.0 mg drospirenone, 0.030 mg ethinyl estradiol, 0.451 mg levomefolate calcium tablets and 0.451 mg levomefolate calcium tablets) but a causal relationship has not been established: acne, anxiety, arthralgia, asthenia, cyst, dysgeusia, full blood count increased, influenza-like illness, muscle spasms, ovarian cyst.

Post-Market Active Surveillance Study

A prospective, controlled, noninterventional, active surveillance cohort study (EURAS) was conducted in Europe to compare risks of adverse cardiovascular and other events associated with the use of DRSP-containing OCs (YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol) and other OCs. (24) In this study, 58,674 OC users were actively followed for a total of 142,475 woman-years. Loss to follow-up was 2.4%. The hazard ratios for venous thromboembolic (VTE) and for all thromboembolic (TE) events were close to 1 and thus do not suggest a higher risk for YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol) users. The results exclude a 1.5-fold thromboembolic risk of YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol) users compared to users of LNG-containing OCs and a 1.2-fold thromboembolic risk compared to users of other OCs. Arrhythmic events that could be suggestive of an increased serum potassium level (eg, because of the antimineralocorticoid activity of DRSP) were not observed in this Postmarket Surveillance study.

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

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

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

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

a YASMIN contains 3.0 mg drospirenone and 0.030 mg ethinyl estradiol

b All thromboembolic events (VTE and ATE combined)

DRUG INTERACTIONS

Overview

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

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

Drug-Drug Interactions

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

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Antibiotics (36)	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.	

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

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants (37-39)	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 µg ethinyl estradiol), another drug, or another non-hormonal method of contraception.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another non-hormonal method of contraception.
Cholesterol lowering agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another non-hormonal method of contraception.
HCV Protease Inhibitors	Boceprevir Telaprevir	Remains to be confirmed	Use another drug or another non-hormonal method of contraception.
HIV protease inhibitors (40)	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Non-nucleoside reverse transcriptase inhibitors (41, 42)	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Sedatives and hypnotics	Barbiturates Benzodiazepines Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional non-hormonal method of contraception or another drug. For long course, use another non-hormonal method of contraception or higher dose oral contraceptives.
Other drugs	Antihistamines Analgesics Antimigraine preparations Phenylbutazone preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

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

Women on short-term treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing orange 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 substances, another form of reliable, non-hormonal, method of contraception is recommended.

Several of the anti-HIV/HCV protease inhibitors (eg, ritonavir, telaprevir, boceprevir) and non-nucleoside 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 progestogen 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, itraconazole, ketoconazole, 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**).

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

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

Table 5 – Modification of Other Drug Action by Oral Contraceptives

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

Table 5 – Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
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 YASMIN® 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.
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).

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 YASMIN® PLUS with other drugs (see **WARNINGS AND PRECAUTIONS**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the YASMIN® clinical trials.

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

Drug-Food Interactions

The effect of food on absorption of drospirenone, ethinyl estradiol and levomefolate calcium following administration of YASMIN 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:

Liver Function Tests

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

Coagulation Tests

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

Thyroid Function Tests

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

Lipoproteins

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

Gonadotropins

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

Glucose Tolerance

Oral glucose tolerance remained unchanged or was slightly decreased.

Vitamin B_{12}

Folates may mask vitamin B_{12} 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 YASMIN 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 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.

Noncontraceptive Benefits of Oral Contraceptives

Several health advantages other than contraception have been reported.

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.
2. Oral contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.
3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.
6. Oral contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.
7. Oral contraceptives have potential beneficial effects on endometriosis.

DOSAGE AND ADMINISTRATION

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

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

The patient begins each subsequent course of YASMIN 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 one or more of her birth control pills. She should be told to match the number of tablets missed with the appropriate starting time for her dosing regimen. The risk of pregnancy increases with each hormone-containing orange tablet missed.

Table 6 – Management of Missed Hormone-Containing Orange Tablets

Sunday Start	Other Than Sunday Start
Miss One Orange Tablet At Any Time	**Miss One Orange 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 Orange Tablets in a Row	**Miss Two Orange 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 pills 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 Week 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**
Miss Three or More Orange Tablets in a Row	**Miss Three or More Orange Tablets in a Row**
Anytime in the cycle 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Anytime in the cycle** 1. Safely dispose of the rest of the 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 the patient forgets any of the seven 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 one 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 YASMIN 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 YASMIN PLUS preferably on the day of removal, but at the latest when the next application would have been due.

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

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

Following delivery or second trimester abortion: Patients should be advised to start YASMIN 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 seven days of YASMIN 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 YASMIN 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 orange tablet. If spotting or breakthrough bleeding occurs while taking YASMIN PLUS, the patient should be instructed to continue taking YASMIN PLUS as instructed and by the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult her physician.

Although the occurrence of pregnancy is unlikely if YASMIN 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 one or more hormone-containing tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

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

Folate Supplementation: Health Canada Prenatal Nutrition Guidelines for Health Professionals and the Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guidelines (43) 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 B_{12}, 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 YASMIN PLUS. Ensure that folate supplementation is maintained if a woman discontinues YASMIN PLUS due to pregnancy or the desire to become pregnant.

OVERDOSAGE

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

There have been no reports of overdose with YASMIN 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 B_{12} deficiency.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

YASMIN PLUS is a combination oral contraceptive consisting of 28 film-coated tablets of which 21 tablets each contain the active ingredients drospirenone, and ethinyl estradiol as betadex clathrate and the vitamin levomefolate calcium (0.451 mg) and 7 tablets each contain the vitamin levomefolate calcium (0.451 mg). (44) 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. (45) Preclinical studies in animals and in vitro have shown that drospirenone has no androgenic, estrogenic, glucocorticoid and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity. (46, 47)

Estrogen-containing combinations such as YASMIN 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 anti-androgenic activity of drospirenone partially counteracts the effects of endogenous androgens, blocking the binding of dihydrotestosterone (DHT) at the receptor level, which makes it a suitable option in the treatment of acne. Drospirenone may also help to reduce edema of the wall of the sebaceous follicle during the second half of the menstrual cycle, which is partly responsible for the flare-up of inflammatory lesions at this cycle phase.

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 B_9. 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 YASMIN 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. (48, 49) The critical time for NTDs is early in pregnancy (the closure of the neural tube is normally completed within 28 days after conception, (50) and achievement of an adequate level of folate takes several weeks.

Pharmacodynamics

Drospirenone inhibits ovulation and follicular development at an oral threshold dose of 2 mg. (51) Drospirenone 3 mg, in combination with ethinyl estradiol 0.030 mg, was found to be optimal for inhibition of ovulation and cycle control.

Drospirenone exhibited aldosterone antagonist activity at doses as low as 2 mg/day in healthy volunteers. Plasma renin activity and plasma aldosterone concentrations were increased, as was the excretion of aldosterone metabolites. The excretion of Na^+ was transiently increased by drospirenone (2 or 3 mg) alone or in combination with ethinyl estradiol (0.030 mg). Serum Na^+ and K^+ concentrations remained unchanged. The potency of drospirenone was 6.6 times higher on average than that of spironolactone, using the Na^+/K^+ urinary ratio as the primary indicator of potency of the aldosterone antagonistic effect.

Drospirenone (2, 3, or 4 mg) in combination with ethinyl estradiol (0.030 mg) displayed a favourable effect on the lipid profile with an increase in HDL and a slight decrease in LDL. Total cholesterol remained unchanged. In addition, oral glucose tolerance remained unchanged or was slightly decreased.

Drospirenone had no effect on the biosynthesis of sex hormone binding globulin (SHBG) and when administered in conjunction with ethinyl estradiol (0.030 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).

Folate Supplementation

The pharmacodynamic study evaluated the impact of YASMIN PLUS on plasma folate and red blood cell (RBC) folate levels. A randomized, double-blind, double dummy, parallel group pharmacodynamic clinical trial compared plasma folate and RBC folate levels during a 24-week treatment period with YASMIN PLUS as compared to YASMIN® (3.0 mg drospirenone/0.030 mg ethinyl estradiol) plus folic acid in healthy female volunteers (see **CLINICAL TRIALS**).

Pharmacokinetics

Table 7: Summary of Pharmacokinetic Parameters of Drospirenone, Ethinyl Estradiol and L-5-methyl-THF after single oral administration of the hormone containing YASMIN PLUS tablet (3 mg DRSP, 0.03 mg EE and 0.451 mg levomefolate calcium) in healthy young women

Parameter	Yasmin Plus (Test) N = 41	Yasmin (Reference) N=41	% Ratio of Geometric Means	Two-sided 90% Confidence Interval
Ethinyl estradiol (1 x 0.030 mg)				
AUC(0-t_{last}) [pg·h/mL]	613.3	607.7	101.1	97.7/104.8
AUC (pg·h/mL)	n/a	n/a	n/a	n/a
C_{max} (pg/mL)	63.2	62.1	102.3	96.7/108.2
t_{max}[a] (h)	2 (1-4) (N=42)	2 (0.5-4) (N=42)	-	-
$t_{½}$ (h)	12.1 (27.6%) (N=17)	12.0 (24.5%) (N=21)	-	-
Drospirenone (1 x 3 mg)				
AUC (0-t_{last}) [ng·h/mL] N=40	416 (22.9%)	402 (30.5%)	n/a	n/a
AUC [ng·h/mL]	453.9	455.2	99.5	96.7/102.3
AUC(0-72h) [ng·h/mL]	368.8 (N=39/38[b])	368.3 (N=39/38b)	99.6	97.3/101.9
C_{max} (ng/mL)	27.5	27.8	98.7	93.4/104.2
t_{max}[a] (h) N=40	1.5 (0.5-3)	1.5 (1-3)	-	-
$t_{½}$ (h) N=40	32.7 (25.0%)	32.3 (24.1%)	-	-

Table 7: Summary of Pharmacokinetic Parameters of Drospirenone, Ethinyl Estradiol and L-5-methyl-THF after single oral administration of the hormone containing YASMIN PLUS tablet (3 mg DRSP, 0.03 mg EE and 0.451 mg levomefolate calcium) in healthy young women

Parameter	Yasmin Plus (Test) N = 41	Yasmin (Reference) N=41	% Ratio of Geometric Means	Two-sided 90% Confidence Interval
L-5-methyl-THF (1 x 0.451 mg)				
		Levomefolate calcium (Reference) N=41		
AUC (0-t_{last}) (nmol·h/L)	394.5	396.0	99.6	95.7/103.7
AUC	n/a	n/a	n/a	n/a
C_{max} (nmol/L)	65.4	62.3	104.9	98.8/111.3
t_{max} [a] (h)	0.5 (0.5-1.5)	0.5 (0.5-1.5) (N=43)	-	-
$t_{½}$ (h)	n/a	n/a	-	-

Abbreviations: AUC = area under the curve; AUC(0-tlast) = area under the concentration-time curve from baseline to last measurement time point; Cmax = maximum concentration attained; h = hour; L = litre; L-5-methyl-THF = L-5-methyltetrahydrofolate; mg = milligram; mL = milliliter; N = number of patients evaluated; n/a = not applicable, ng = nanogram; nmol = nanomoles; pg = pictogram; t1/2 = half time; tmax = time at which maximum concentration is achieved

a Expressed as median (range)

b One subject excluded due to missing 72 h measurement

Table 8 - Summary of Pharmacokinetic Parameters of L-5-methyl-THF after single oral administration of the hormone free YASMIN 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	43	61.8 (29.2%)	390 (33.2%)	0.5 (0.5-1.5)
L-5-methyl-THF	corrected	43	48.7 (30.4%)	239 (26.5%)	0.5 (0.5-1.5)

Abbreviations: AUC = area under the curve, C_{max} = maximum concentration, h = hour, L-5-methyl-THF = L-5-methyltetrahydrofolate, L = liter, N = number of subjects, nmol = nanomoles, 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.

YASMIN® PLUS and YASMIN® have been shown to be equivalent with respect to DRSP and EE.

Absorption

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

After single oral administration of YASMIN PLUS, the mean maximum concentration of EE was 63.2 pg/mL and was reached 2 hours after administration. For DRSP, the mean maximum concentration was 27.5 ng/mL and was reached 1.5 hours after administration (see Table 7 above).

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol), steady state DRSP concentrations were observed after 10 days. There was about 2- to 3-fold accumulation in serum C_{max} and $AUC_{(0-24h)}$ values of DRSP following multiple-dose administration of YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of YASMIN (3.0 mg drospirenone, 0.030 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 50 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 8 above) or in combination with EE/DRSP (see Table 7 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 two YASMIN (3.0 mg drospirenone, 0.030 mg ethinyl estradiol) tablets was slower under fed conditions, with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

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

Distribution

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

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

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

EE is subject to significant gut and hepatic first-pass metabolism. EE and its oxidative metabolites are primarily conjugated with glucuronides or sulfate. CYP3A4 in the liver is 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 ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38% to 47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17% to 20% of the metabolites were excreted as glucuronides and sulfates.

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

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.

Special Populations and Conditions

Pediatrics

The safety and efficacy of YASMIN 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

YASMIN PLUS is not indicated for use in postmenopausal women.

Race

The effect of race on the disposition of YASMIN PLUS has not been evaluated.

Hepatic Insufficiency

YASMIN PLUS is contraindicated in patients with hepatic dysfunction (see **WARNINGS AND PRECAUTIONS**). The mean terminal half-life of DRSP for women with moderate hepatic impairment was 1.8 times greater than for women with normal hepatic function.

Renal Insufficiency

YASMIN PLUS is contraindicated in patients with renal insufficiency (see **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 five of the seven subjects who continued use of potassium-sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range and who are concomitantly using potassium sparing drugs.

STORAGE AND STABILITY

Store in original packaging between 15°C and 25°C; protect from moisture and heat.

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

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

YASMIN PLUS

Each blister pack contains 21 hormone-containing orange and 7 hormone-free light-orange, film-coated, round tablets. The 7 hormone-free tablets contain folate (levomefolate calcium).

Each hormone-containing orange, film-coated tablet contains 3.0 mg drospirenone, 0.030 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 “Y+” in a regular hexagon.

The light-orange tablets are hormone-free and contain 0.451 mg levomefolate calcium. The hormone-free tablet is round with convex faces, one side embossed with the letters "M+" in a regular hexagon.

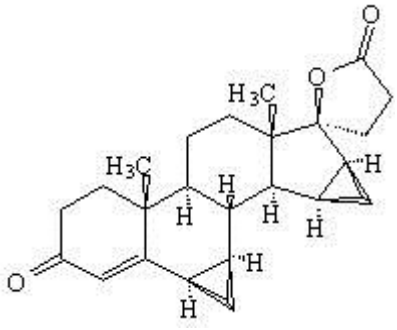
Nonmedicinal ingredients for both hormone-containing and hormone-free (folate containing) tablets: microcrystalline cellulose, croscarmellose sodium, ferric oxide red, ferric oxide yellow, hydroxypropylcellulose 5 cP, hypromellose 5 cP, lactose monohydrate, macrogol 6000, magnesium stearate, talc, titanium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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Drospirenone:

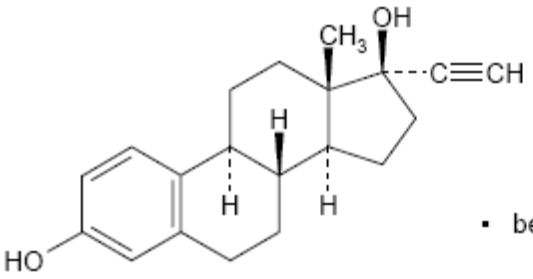
Proper Name:	drospirenone
Chemical Name:	6β, 7β; 15β, 16β-dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone (IUPAC) [6R-(6α, 7α, 8β, 9α, 10β, 13β, 14α, 15α, 16α, 17β]-1,3′,4′,6, 7,8,9,10,11,12,13,14,15,16,20,21-hexadecahydro-10,13-dimethylspiro[17*H*-dicyclopropa[6,7:15, 16] cyclopenta[α]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione (USAN)
Structural Formula:	
Molecular Formula:	$C_{24}H_{30}O_3$
Molecular Weight:	366.50
Description:	White to off-white crystalline powder. Freely soluble in dichloromethane; soluble in acetone, methanol, ethyl acetate, dimethoxyethane, and toluene; sparingly soluble in ethanol, and practically insoluble in water, n-hexane and diisopropyl ether. Melting range is 199°C to 201°C.
pKa:	Neutral molecule without any acid-base properties in aqueous solutions (pH 1 to 12)
Partition coefficient:	log P_{OW} = 3.08

Ethinyl estradiol:

Proper Name: ethinyl estradiol (as betadex clathrate)

Chemical Name: 19-nor-17α-pregna-1,3,5(10)-triene-20-yne-3,17-diol Bis(β-cyclodextrin-clathrate) (IUPAC)

Structural Formula:



▪ beta-Cyclodextrin-clathrate 1:2

Molecular Formula: $C_{104}H_{164}O_{72}$

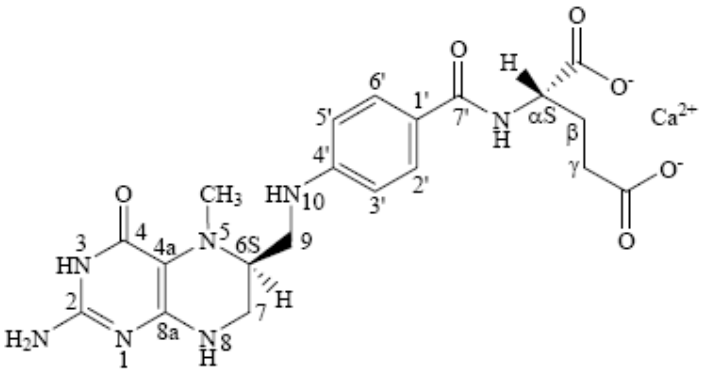
Molecular Weight: 2566.4

Description: White to off-white powder. The aqueous solubility of ethinyl estradiol (as betadex clathrate) is 3.7 g/L. Due to decomposition, no melting point or range can be determined.

pKa: 10.51 ± 0.03

Partition Coefficient: log P_{OW} = 3.38 (pH=5)
3.53 (pH=7)
3.20 (pH=9)

Levomefolate calcium:

Proper Name:	levomefolate calcium
Chemical Name:	N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridinyl)methyl]amino]benzoyl]-L-glutamic acid, calcium salt
Structural Formula:	
Molecular Formula:	Calcium salt: $C_{20}H_{23}CaN_7O_6$ Free acid: $C_{20}H_{25}N_7O_6$
Molecular Weight:	Calcium salt: 497.52 g/mol Free acid: 459.46 g/mol
Physicochemical Properties:	White to yellow or beige powder. Practically insoluble in most apolar and polar organic solvents. Melting point approximately 300°C. Sparingly soluble in water.

CLINICAL TRIALS

Contraception

The contraceptive efficacy of YASMIN® (drospirenone and ethinyl estradiol) was demonstrated in three pivotal, open-label, multicentre, clinical trials conducted in women 16 to 40 years of age (see Table 9 below).

Table 9 – Contraceptive Efficacy of YASMIN in 3 Pivotal Clinical Trials

	Study 1 (52)	Study 2 (53)	Study 3 (54)
Corrected[a] Pearl Index			
Number of cycles	3192	18418	9490
Number of pregnancies	1	10	3
Pearl Index	0.41	0.71	0.41
Corrected[a] Pregnancy Ratio			
Cycles completed/subject	13	13	26
Number of subjects	220	1186	268
Number of pregnancies	1	10	3
Pregnancy Ratio (%)	0.46	0.84	1.18

a Corrected to exclude concomitant use of other contraceptives

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

Acne Therapy

The efficacy of YASMIN in treating moderate acne was demonstrated in two pivotal, double-blind, comparative, multicentre clinical trials in women 16 to 40 years of age.

Study A07158

The primary objectives of the study were to compare the efficacy of YASMIN with a triphasic preparation containing 0.035 mg ethinyl estradiol and 0.180, 0.215, 0.250 mg norgestimate (EE/NGM), in terms of relative change in inflammatory lesion count in percent (papules + pustules + nodules), relative changes in total lesion count in percent (papules + pustules + nodules + open and closed comedones), and the proportion of subjects who showed improvement of their facial acne according to the investigator's global assessment from randomization to Cycle 6. (55)

Female subjects were randomized to YASMIN (n = 568) or EE/NGN (n = 586) for 6 treatment cycles.

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

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

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

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

Study AM80

This multicentre, double-blind, randomized study compared the effect of YASMIN with that of 0.035 mg ethinyl estradiol/2 mg cyproterone acetate (EE/CPA). (56) The study was completed over 9 treatment cycles. A total of 128 women with acne (aged 16-33 with a minimum of 8 papulopustular lesions on the face) were randomized. Treatment with either YASMIN (n = 82) or EE/CPA (n = 43) was assigned in a 2:1 ratio. Acne lesion count was assessed as the primary variable. After nine treatment cycles, the mean number of acne lesions was reduced by 37.51% in the YASMIN group and 35.03% in the EE/CPA group in the intent-to-treat (ITT) population (*P* value from Wilcoxon test = 0.0006).

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

Folate Supplementation

Study Demographics and Trial Design

The clinical development program for YASMIN PLUS for the improvement of folate status in women who elect to use oral contraception consisted of a clinical trial carried out in Germany. An overview of the study is presented below in Table 10.

Table 10 - Overview of the Study Evaluating the Efficacy of YASMIN 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]
309763	Pharmacodynamic Clinical Single-center, randomized, double blind, double dummy, parallel group pharmacodynamic clinical trial	Oral/ One medicated tablet daily for 24 weeks followed by 20 weeks of open-label treatment with YASMIN only	Test product: YASMIN PLUS (DRSP 3 mg + EE 0.030 mg + 0.451 mg levomefolate calcium and 0.451 mg levomefolate calcium)	86	28.4 (18-40)	23.2 ± 2.7
			Comparator: YASMIN® (DRSP 3 mg + EE 0.030 mg)	86	27.0 (18-40)	22.4 ± 2.6

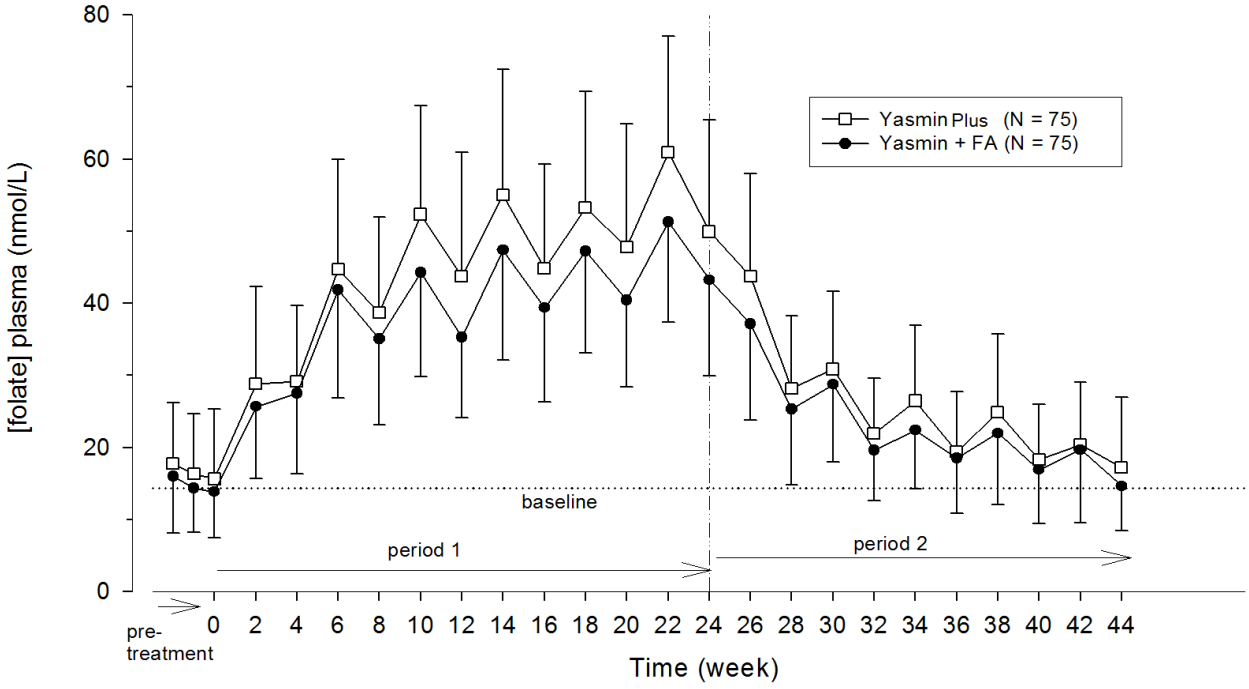
Abbreviations: BMI = Body Mass Index, DRSP = drospirenone, EE = ethinyl estradiol, kg = kilogram, m = meter, mg = milligram
a Full analysis set (FAS)
b Subjects with BMI > 30 kg/m^2 were excluded from this study

Study Results

Study 309763

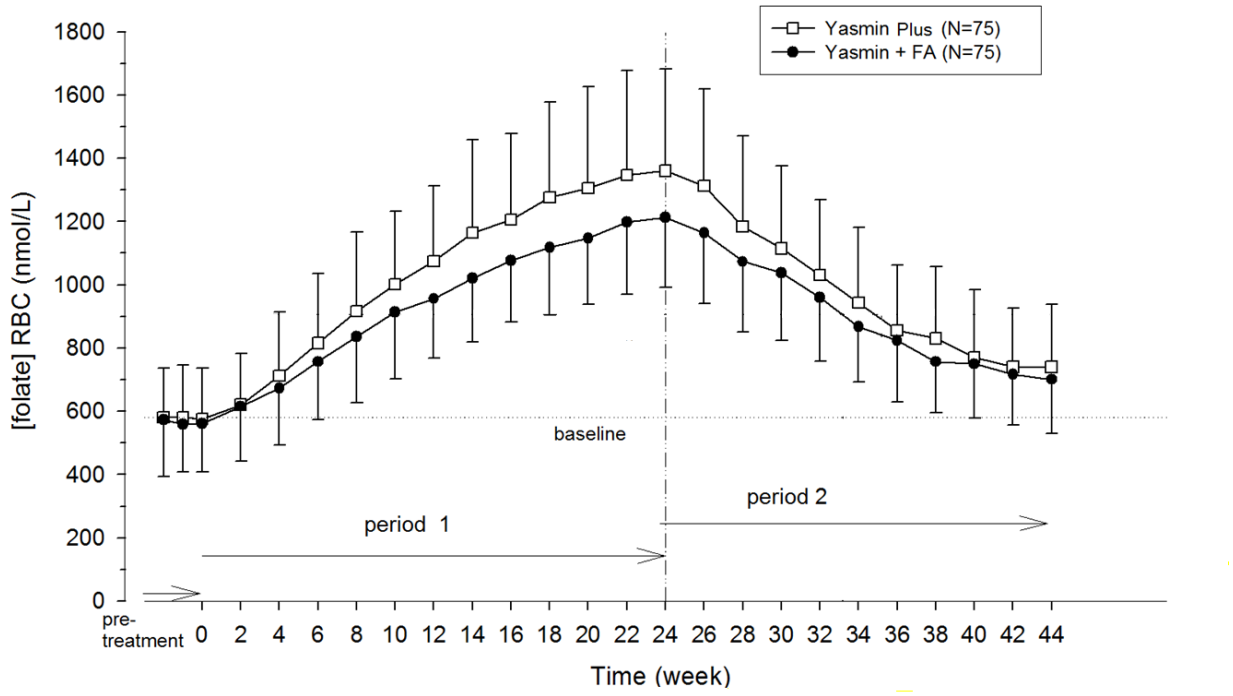
Study 309763 was a single-center, randomized, double-blind, double-dummy, 2 parallel arm study conducted in Germany. Plasma folate and red blood cell (RBC) folate levels were investigated during a 24-week treatment period with YASMIN PLUS as compared to YASMIN® co administered with folic acid (YASMIN® + FA) followed by 20 weeks of open-label treatment with YASMIN® only (ie, folate elimination phase). A total of 172 healthy women between 18 and 40 years of age from a German population that consumed food without folate fortification, with RBC folate levels between 317 nmol/L and 906 nmol/L, no concomitant intake of vitamin supplements or medication containing folate, or that interact with folate, and no vitamin B12 deficiency received YASMIN PLUS (n=86) or YASMIN® + FA (n=86). 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 309763 – Mean concentration-time curves (and SD) of plasma folate after daily oral administration of YASMIN PLUS and YASMIN® + Folic Acid



Abbreviations: FA = folic acid, L = litre, nmol = nanomole
Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. In period 1, women were treated with YASMIN PLUS, or YASMIN + FA; in period 2, all women received YASMIN only.
Data are based on per protocol analysis populations.

Figure 2: Study 309763- Mean concentration-time curves (and SD) of RBC folate after daily oral administration of YASMIN PLUS and YASMIN® + Folic Acid



Abbreviations: FA = folic acid, L = litre, nmol = nanomole, RBC = red blood cell
Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. In period 1, women were treated with YASMIN PLUS or YASMIN® + FA; in period 2, all women received YASMIN® only.
Data are based on per protocol analysis populations.

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. (49, 57, 58) Therefore, Health Canada Prenatal Nutrition Guidelines for Health Professionals and the Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guidelines (43) recommend that women of childbearing age consume supplemental folic acid in a minimum dose of 0.4 mg (400 µg) daily.

DETAILED PHARMACOLOGY

Animal Pharmacology

Drospirenone

Drospirenone exhibits potent progestational activity in a variety of animal models. In ovariectomized pregnant rats treated with drospirenone 3 mg/day SC in combination with ethinyl estradiol 0.1 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 (0.3-10 mg/day for 7 days) dose-dependently inhibited testosterone-induced growth of the seminal vesicle and prostate in castrated, testosterone-substituted rats. This activity does not appear to be centrally mediated in rats because decreases in the relative weights of male accessory sex organs occur in the absence of significant changes in testes weights or serum luteinizing hormone levels. Oral or subcutaneous administration of drospirenone (10 mg/day) to pregnant rats during the final trimester of pregnancy resulted in the feminization of male fetuses, characterized by a significant shortening of the anogenital distance and the length of the urethra.

Significant antimineralocorticoid activity, characterized by increased sodium excretion and an increase of the urinary Na+/K+ ratio, was observed following single oral or subcutaneous administration of drospirenone to adrenalectomized, aldosterone-substituted rats. Drospirenone was five to ten times more potent than spironolactone, and its aldosterone antagonist activity was not affected by concomitant administration of ethinyl estradiol. (59) When administered for 21 days to ovariectomized female rats, drospirenone (10 mg/day) stimulated the Na+/K+ excretion ratio over the entire treatment period, while spironolactone (10 mg/day) became ineffective after the initial treatment phase due to counter-regulation. Drospirenone also exhibited significant antimineralocorticoid activity in vitro, inhibiting aldosterone-stimulated electrogenic sodium transport 10 times more effectively than either spironolactone or progesterone. In vitro, drospirenone binds with high affinity to the mineralocorticoid receptor.

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

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

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

Ethinyl Estradiol

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

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

TOXICOLOGY

Acute Toxicity

Table 11 below summarizes the median lethal doses (LD_{50}) determined in acute toxicity studies with drospirenone.

Table 11 – LD_{50} Values for Drospirenone

Species	Doses Tested (mg/kg/day)	Route of Administration	LD_{50} (mg/kg)
Mouse	0, 250, 500, 1250, 2500	Intragastric	500-2500
	0, 250, 500, 1250, 2500	Intraperitoneal	250-500
Rat	0, 250, 500, 1250, 2000	Intragastric	500 - 1250
	0, 100, 250, 500, 1250, 2000	Intraperitoneal	100 - 250
Dog	0, 250	Oral (capsules)	> 250
	0, 0.165	Intravenous	>0.165

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

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

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 intragastric administration of the following doses.

Table 12 – Long-term Toxicity Studies Conducted With Drospirenone (DRSP) and Ethinyl Estradiol (EE)

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

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

Changes observed following administration of drospirenone alone included:

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

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

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

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

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 13 - Carcinogenicity Studies Conducted with Drospirenone (DRSP) and Ethinyl Estradiol (EE)

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

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

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

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

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

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

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

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 14 - Reproductive Toxicity Studies Conducted With Drospirenone (DRSP) + Ethinyl Estradiol (EE)

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

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

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

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

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 15-18 of gestation and Days 1-22 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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrYASMIN® PLUS
Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets

Read this carefully before you start taking **YASMIN PLUS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **YASMIN PLUS**.

Serious Warnings and Precautions

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

- Birth control pills **DO NOT PROTECT** against sexually transmitted infections (STIs), including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

What is YASMIN PLUS used for?

- To prevent pregnancy
- To treat moderate acne in women 16 years of age and older who are able to use birth control pills and have achieved menarche. Your first menstrual period is referred to as menarche.
- To improve folate levels in women who choose to use an oral contraceptive.

How does YASMIN PLUS work?

YASMIN PLUS is a birth control pill (oral contraceptive) that contains two female sex hormones (drospirenone and ethinyl estradiol). YASMIN PLUS also contains levomefolate calcium, which is a B vitamin. When taken as prescribed by your doctor, YASMIN PLUS has been shown to be highly effective in preventing pregnancy. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.

Birth control pills work in two ways:

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

Drospirenone in YASMIN PLUS helps with androgen (male sex hormone) related skin problems. Androgen circulates naturally within the female body. Androgens can cause glands in

the skin to over-produce oil. This results in acne. YASMIN PLUS works by lowering androgen levels in the body and by blocking the effects of androgens at the gland. As a result, a reduction in the number of acne breakouts is associated with YASMIN PLUS treatment.

Levomefolate calcium in YASMIN PLUS provides folate supplementation in women who choose to use an oral contraceptive. It is recommended that women who could become pregnant supplement their diet with a minimum of 0.4 mg (400 µg) of folic acid daily to lower the risk of having a pregnancy with a rare type of birth defect (known as a neural tube defect).

Effectiveness of Birth Control Pills

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

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

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

The chance of becoming pregnant increases with incorrect use.

Other Ways to Prevent Pregnancy

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

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

Reported Pregnancies per 100 Women per Year:	
Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

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

The effective use of birth control methods other than birth control pills and IUDs requires more effort than taking a single pill every day. It is an effort that many couples undertake successfully.

What are the ingredients in YASMIN PLUS?

Medicinal ingredients: Drospirenone, ethinyl estradiol and levomefolate calcium
Non-medicinal ingredients: cellulose microcrystalline, croscarmellose sodium, ferric oxide red, ferric oxide yellow, hydroxypropylcellulose 5 cP, hypromellose 5 cP, lactose monohydrate, macrogol 6000, magnesium stearate, talc, and titanium dioxide.

YASMIN PLUS comes in the following dosage forms:

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

Each blister pack contains 21 hormone-containing orange and 7 hormone-free light-orange, film-coated, round tablets. Each hormone-containing orange, film-coated tablet contains 3.0 mg drospirenone, 0.030 mg ethinyl estradiol and 0.451 mg levomefolate calcium. The light-orange tablets are hormone free and contain 0.451 mg levomefolate calcium.

Do not use YASMIN PLUS if:

- You have or have had blood clots in the legs, lungs, eyes, or elsewhere, or thrombophlebitis (inflammation of the veins)
- You have or have had stroke, heart attack, or coronary artery disease (eg, angina pectoris), or a condition that may be a first sign of a stroke (such as a transient ischemic attack or small reversible stroke)
- You have or have had disease of the heart valves with complications
- You have or have had known abnormalities of the blood clotting system that increases your risk for developing blood clots
- You have severe high blood pressure
- You have diabetes with complications
- You have very high blood cholesterol or triglyceride levels
- You smoke and are over age 35
- You have migraine headache
- You are scheduled for major surgery
- Prolonged bed rest
- You are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C
- You have jaundice (yellowing of the eyes or skin), liver disease or liver tumor

- You have known or suspected cancer of the breast or uterus (womb) or other estrogen-dependent cancer
- You have unusual vaginal bleeding without a known reason
- You have loss of vision due to blood vessel disease of the eye
- You are pregnant or suspect you may be pregnant
- You have pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood
- You have allergy (hypersensitivity) to drospirenone ethinyl, estradiol, levomefolate calcium, or to any of the other ingredients in YASMIN PLUS (see What are the ingredients in YASMIN PLUS?)

In addition, do not use YASMIN PLUS if:

- You have kidney disease
- You have liver disease
- You have adrenal disease

YASMIN PLUS is a birth control pill containing estrogen and progestogen and a vitamin (levomefolate calcium). The progestogen in YASMIN PLUS is known as drospirenone and it may increase potassium. Therefore, you should not take YASMIN PLUS if you have kidney, liver, or adrenal disease (a disease that may alter the body's fluid and mineral balance) because this could cause serious heart and health problems. Other drugs may also increase potassium (see To help avoid side effects and ensure proper use, talk to your healthcare professional before you take YASMIN PLUS. Talk about any health conditions or problems you may have, including if you:). During the first month that you take YASMIN PLUS, you should have a blood test to check your potassium level.

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

It has been reported that drospirenone, the progestogen in YASMIN PLUS, may carry a higher risk of blood clots than some other progestogens (including levonorgestrel). You should talk to your doctor about the available options.

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

- smoke
- are overweight
- have a history of breast disease (eg, breast lumps) or a family history of breast cancer
- have high blood pressure

- have high cholesterol
- have diabetes
- have heart or kidney disease
- have a history of seizures/epilepsy
- have a history of depression
- have a history of liver disease or jaundice
- wear contact lenses
- have uterine fibroids (benign tumors of the uterus)
- may be pregnant or are breast feeding
- have systemic lupus erythematosus
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have hemolytic uremic syndrome
- have sickle cell disease
- have any problems with the valves in your heart and/or have an irregular heart rhythm
- if you suffer from vitamin B_{12} deficiency (for example due to a reduced B_{12} diet such as a strict vegetarian diet, due to a history of gastrointestinal surgery or certain types of gastritis) tell your doctor that you use YASMIN PLUS because folates may hide vitamin B_{12} deficiency
- have been told that you have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, or airway passages
- **you are currently on daily, long-term treatment for a chronic condition with any of the medications listed below:**
  - **Nonsteroidal anti-inflammatory drugs (NSAIDs) when taken long-term and for treatment of arthritis or other problems (eg, ibuprofen, naproxen or others)**
  - **Potassium-sparing diuretics (spironolactone and others)**
  - **Potassium supplements**
  - **ACE inhibitors and Angiotensin-II receptor antagonists for the treatment of high blood pressure (eg, captopril, enalapril, lisinopril, losartan, valsartan, irbesartan, or others)**
  - **Heparin**

Other warnings you should know about:

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

Inform your doctor if you are taking daily folate supplements.

YASMIN PLUS contains the equivalent of 0.4 mg of folic acid.

If you see a different doctor, inform him or her that you are using YASMIN PLUS.

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

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

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

If you and your doctor decide that, for you, the benefits of YASMIN PLUS outweigh the risks, you should be aware of the following:

THE RISKS OF USING YASMIN PLUS

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

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

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

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

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

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

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

2. Breast cancer

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

Some women who use hormonal contraceptives may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term users of birth control pills (more than eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small, however. A yearly breast examination by a health care professional is recommended for all women.

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

3. Cervical cancer

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

4. Liver tumors

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

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

5. Gallbladder disease

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

6. Use in pregnancy

Birth control pills should not be taken by pregnant women. There is no evidence, however, that the birth control pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy. Also, check with your doctor about appropriate folate supplementation if you stop taking YASMIN PLUS, are pregnant, or plan on becoming pregnant.

7. Use after pregnancy, miscarriage, or an abortion

Your doctor will advise you of the appropriate time to start the use of YASMIN PLUS after childbirth, miscarriage, or therapeutic abortion.

8. Pregnancy after stopping YASMIN PLUS

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

9. Use while breast feeding

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

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

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

The following may interact with YASMIN PLUS:

- drugs used for the treatment of epilepsy (eg, primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate, phenobarbital, valproic acid); tuberculosis (eg, rifampin, rifabutin), HIV infections (eg, ritonavir, nevirapine), and Hepatitis C Virus Infections (eg, boceprevir, telaprevir)
- antibiotics (eg, penicillins, tetracyclines, clarithromycin, erythromycin) for infectious diseases
- cyclosporine
- ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (used to treat Hepatitis C)
- antifungals (griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole)
- cholesterol-lowering drugs (eg, clofibrate)
- drugs used for the treatment of certain heart diseases or high blood pressure (eg, diltiazem, verapamil)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (eg, benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (meperidine)
- antidepressants (eg, clomipramine)

- tizanidine (drug used for multiple sclerosis [MS])
- theophylline (drug used for asthma)
- some nutritional supplements (eg, Vit. B_{12}, folic acid)
- antacids (use 2 hours before or after taking YASMIN PLUS)
- drugs that may decrease folate levels (eg, methotrexate, trimethoprim, sulfasalazine, triamteren, cholestyramine, and antiepileptic drugs listed above)

YASMIN PLUS may also interfere with the working of other drugs.

Herbal or food products that may interact with YASMIN PLUS include:

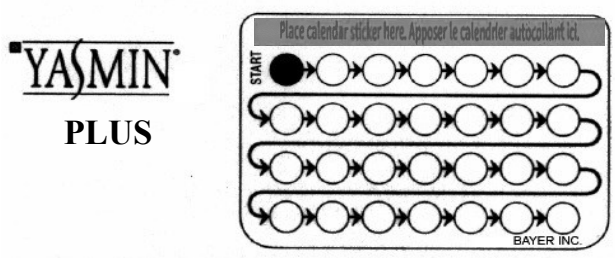
- the herbal remedy St. John's wort (primarily used for the treatment of depressive moods)
- grapefruit juice

This is not a complete list of possible drug interactions with YASMIN PLUS. Talk to your doctor for more information about drug interactions.

How to take YASMIN PLUS:

Usual dose:

1. **READ THESE DIRECTIONS**
   - before you start taking your pills, and
   - any time you are not sure what to do.
2. **LOOK AT YOUR PILL PACK** it has 28 pills;
   The YASMIN PLUS pill pack has 21 hormone-containing orange pills taken daily for three weeks, and then seven hormone-free light-orange pills taken daily for one week. **It is important to take the light-orange pills because they contain folate.**



   ALSO CHECK the pill pack for: 1) where to start and 2) direction to take pills in (follow the arrows).
3. You should use a second method of birth control (eg, latex or polyurethane condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.
4. **When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**

5. **IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES**, such as antibiotics, your pills may not work as well. Use a back-up method, such as latex or polyurethane condoms and spermicidal foam or gel, until you can check with your doctor or clinic.
6. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.
7. Take the pills only on the advice of your doctor and carefully follow all directions given to you. You must take the pills exactly as prescribed. Otherwise, you may become pregnant.
8. Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.
9. **THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.**
10. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:

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

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.
2. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS**. Your period should occur during the last seven days of using that pill pack.

WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
   - Try to associate taking your pill with some regular activity, such as eating a meal or going to bed.
   - Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
   - Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK**

   Start the next pack **ON THE NEXT DAY**. Take one pill every day. **It is important to take the light-orange pills because they contain folate.** Do not wait any days between packs.

Overdose:

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

If you think you have taken too much YASMIN PLUS, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

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

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

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

WHAT TO DO IF YOU MISS PILLS

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

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

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

NOTE: If you forget any of the seven hormone-free light-orange pills (containing folate) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand

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

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

Noncontraceptive Benefits of Birth Control Pills

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

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

What are possible side effects from using YASMIN PLUS?

These are not all the possible side effects you may feel when taking YASMIN PLUS. If you experience any side effects not listed here, contact your healthcare professional. Please also see **WARNINGS AND PRECAUTIONS**.

The following side effects have been observed in studies of women taking YASMIN PLUS which may or may not be drug related:

Most side effects when using the birth control pill are not serious. The most common side effects are nausea, vomiting, bleeding or spotting between menstrual periods, breast pain, acne, itching, migraine, dizziness, emotional lability, dysmenorrhea (painful menstrual cramps), headache, vaginal yeast infection, depression, back pain, abdominal pain, nervousness, rash.

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

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

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

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

- allergy, fatigue, fever
- diarrhea, flatulence
- rash

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON Abdominal pain, nausea or vomiting or lump in the abdomen		✓	
Breast lump		✓	
Crushing chest pain or heaviness			✓
Pain or swelling in the leg			✓
Persistent sad mood			✓
Sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
Sudden partial or complete loss of vision or double vision			✓
Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm, or leg			✓
Unexpected vaginal bleeding		✓	
Unusual swelling of the extremities		✓	
Yellowing of the skin or eyes (jaundice)			✓

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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

Storage:

Store in original packaging between 15ºC and 25ºC, protect from moisture and heat.

Keep out of sight and reach of children and pets.

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

If you want more information about YASMIN PLUS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.bayer.ca, or by calling Bayer Medical Information at 1-800-265-7382 or contacting canada.medinfo@bayer.com.

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