
The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it on October 2014

Yasmin Plus

Film coated tablets

Drospirenone 3 mg

Ethinylestradiol as betadex calthrate 0.03 mg

Levomefolate calcium 0.451 mg

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke [see Contraindications (4)].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Yasmin Plus is indicated for use by women to prevent pregnancy.

1.2 Folate Supplementation

Yasmin Plus is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Yasmin Plus

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

To achieve maximum contraceptive effectiveness, Yasmin Plus must be taken as directed, in the order directed on the blister pack. Single missed pills should be taken as soon as remembered.

2.2 How to Start Yasmin Plus

Instruct the patient to begin taking Yasmin Plus either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start

During the first cycle of Yasmin Plus use, instruct the patient to take one orange Yasmin Plus daily, beginning on Day 1 of her menstrual cycle. (The first day of menstruation is Day 1.) She should take one orange Yasmin Plus daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on Days 22 through 28. Yasmin Plus should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Yasmin Plus can be taken without regard to meals. If Yasmin Plus is first taken later than the first day of the menstrual cycle, Yasmin Plus should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

During the first cycle of Yasmin Plus use, instruct the patient to take one orange Yasmin Plus daily, beginning on the first Sunday after the onset of her menstrual period. She should take one orange Yasmin Plus daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on Days 22 through 28. Yasmin Plus should be

taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Yasmin Plus can be taken without regard to meals. Yasmin Plus should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Yasmin Plus on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her orange tablets on the next day after ingestion of the last light orange folate tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Yasmin Plus is started later than the day following administration of the last light orange tablet, the patient should use another method of contraception until she has taken an orange Yasmin Plus daily for seven consecutive days.

When switching from a different birth control pill

When switching from another birth control pill, Yasmin Plus should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When switching from a method other than a birth control pill

When switching from a transdermal patch or vaginal ring, Yasmin Plus should be started when the next application would have been due. When switching from an injection, Yasmin Plus should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Yasmin Plus should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last orange tablet. If spotting or breakthrough bleeding occurs while taking Yasmin Plus, instruct the patient to continue taking Yasmin Plus by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Yasmin Plus is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Yasmin Plus if pregnancy is confirmed.

The risk of pregnancy increases with each active orange tablet missed. For additional patient instructions regarding missed pills, see the **“WHAT TO DO IF YOU MISS PILLS”** section in the **FDA-Approved Patient Labeling**. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more light orange tablets, she should still be protected against pregnancy provided she begins taking a new cycle of orange tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Yasmin Plus no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts Yasmin Plus postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Yasmin Plus for 7 consecutive days.

2.3 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, this can be regarded as a missed tablet.

2.4 Folate Supplementation

The U.S. Preventive Services Task Force recommends that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily.¹ Consider other folate supplementation 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.

3 DOSAGE FORMS AND STRENGTHS

Yasmin Plus (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in blister packs.

Each blister pack contains 28 film-coated, round, bi-convex tablets in the following order:

- 21 orange tablets each containing 3 mg drospirenone (DRSP), 0.03 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium embossed with a “Y+” in a regular hexagon on one side
- 7 light orange tablets each containing 0.451 mg levomefolate calcium embossed with a “M+” in a regular hexagon on one side

4 CONTRAINDICATIONS

Do not prescribe Yasmin Plus to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35 [see *Boxed Warning and Warnings and Precautions (5.1)*]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [see *Warnings and Precautions (5.1)*]
 - Have cerebrovascular disease [see *Warnings and Precautions (5.1)*]
 - Have coronary artery disease [see *Warnings and Precautions (5.1)*]
 - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see *Warnings and Precautions (5.1)*]
 - Have inherited or acquired hypercoagulopathies [see *Warnings and Precautions (5.1)*]
 - Have uncontrolled hypertension [see *Warnings and Precautions (5.5)*]
 - Have diabetes mellitus with vascular disease [see *Warnings and Precautions (5.7)*]
 - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [see *Warnings and Precautions (5.8)*]
- Undiagnosed abnormal uterine bleeding [see *Warnings and Precautions (5.9)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [see *Warnings and Precautions (5.3)*]
- Liver tumor (benign or malignant) or liver disease [see *Warnings and Precautions (5.4)* and *Use in Specific Populations (8.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [see *Warnings and Precautions (5.10)* and *Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Yasmin Plus if an arterial or venous thrombotic (VTE) event occurs.

Based on presently available information on DRSP-containing COCs with 0.03 mg ethinyl estradiol (that is, Yasmin), DRSP-containing COCs may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing the progestin levonorgestrel or some other progestins. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase. Before initiating use of Yasmin Plus in a new COC user or a woman who is switching from a contraceptive that does not contain DRSP, consider the risks and benefits of a DRSP-containing COC in light of her risk of a VTE. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs [see *Contraindications (4)*].

A number of studies have compared the risk of VTE for users of Yasmin (which contains 0.03 mg of EE and 3 mg of DRSP) to the risk for users of other COCs, including COCs containing levonorgestrel. Those that were required or sponsored by regulatory agencies are summarized in Table 1.

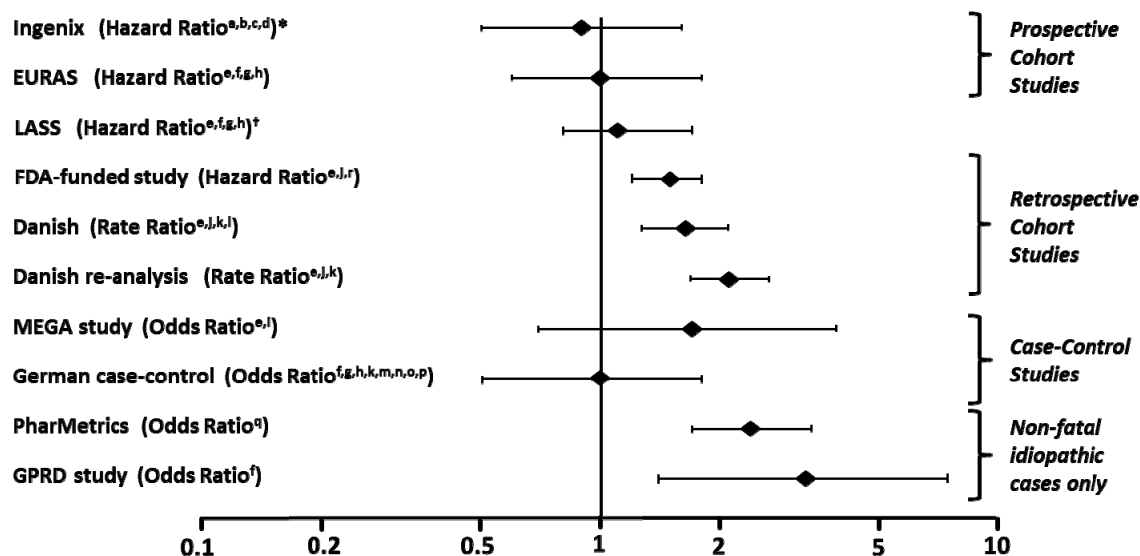
Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Current Users of Yasmin Compared to Users of Oral Contraceptives that Contain Other Progestins

Epidemiologic Study (Author, Year of Publication) Population Studied	Comparator Product (all are low-dose COCs; with ≤ 0.04 mg of EE)	Hazard Ratio (HR) (95% CI)
i3 Ingenix (Seeger 2007) Initiators, including new users ^a	All COCs available in the US during the conduct of the study ^b	HR: 0.9 (0.5-1.6)
EURAS (Dinger 2007) Initiators, including new users ^a	All COCs available in Europe during the conduct of the study ^c	HR: 0.9 (0.6-1.4)
	Levonorgestrel/EE	HR: 1.0 (0.6-1.8)
“FDA-funded study” (2011) New users ^a All users (i.e., initiation and continuing use of study combination hormonal contraception)	Other COCs available during the course of the study ^d	HR: 1.8 (1.3-2.4)
	Levonorgestrel/0.03 mg EE	HR: 1.6 (1.1-2.2)
	Other COCs available during the course of the study ^d	HR: 1.7 (1.4-2.1)
	Levonorgestrel/0.03 mg EE	HR: 1.5 (1.2-1.8)

- a) “New users” - no use of combination hormonal contraception for at least the prior 6 months
- b) Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, levonorgestrel, desogestrel, norgestrel, medroxyprogesterone, or ethynodiol diacetate
- c) Includes low-dose COCs containing the following progestins: levonorgestrel, desogestrel, dienogest, chlormadinone acetate, gestodene, cyproterone acetate, norgestimate, or norethindrone
- d) Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel

In addition to these “regulatory studies,” other studies of various designs have been conducted. Overall, there are two prospective cohort studies (see Table 1): the US post-approval safety study Ingenix [Seeger 2007], the European post-approval safety study EURAS (European Active Surveillance Study) [Dinger 2007]. An extension of the EURAS study, the Long-Term Active Surveillance Study (LASS), did not enroll additional subjects, but continued to assess VTE risk. There are three retrospective cohort studies: one study in the US funded by the FDA (see Table 1), and two from Denmark [Lidegaard 2009, Lidegaard 2011]. There are two case-control studies: the Dutch MEGA study analysis [van Hylckama Vlieg 2009] and the German case-control study [Dinger 2010]. There are two nested case-control studies that evaluated the risk of non-fatal idiopathic VTE: the PharMetrics study [Jick 2011] and the GPRD study [Parkin 2011]. The results of all of these studies are presented in Figure 1.

Figure 1: VTE Risk with Yasmin Relative to LNG-Containing COCs (adjusted risk[#])



Risk ratios displayed on logarithmic scale; risk ratio < 1 indicates a lower risk of VTE for DRSP, > 1 indicates an increased risk of VTE for DRSP.

*Comparator "Other COCs", including LNG- containing COCs

† LASS is an extension of the EURAS study

[#]Some adjustment factors are indicated by superscript letters: a) Current heavy smoking, b) hypertension, c) obesity, d) family history, e) age, f) BMI, g) duration of use, h) VTE history, i) period of inclusion, j) calendar year, k) education, l) length of use, m) parity, n) chronic disease, o) concomitant medication, p) smoking, q) duration of exposure, r) site

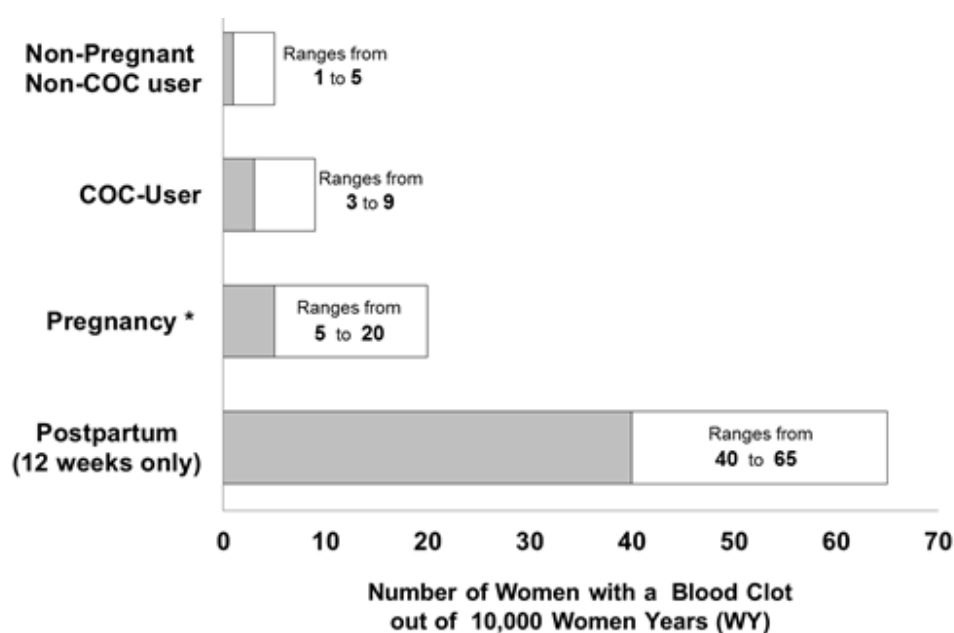
(References: Ingenix [Seeger 2007]², EURAS (European Active Surveillance Study) [Dinger 2007]³, LASS (Long-Term Active Surveillance Study) [Dinger, unpublished document on file], FDA-funded study [Sidney 2011]⁴, Danish [Lidegaard 2009]⁵, Danish re-analysis [Lidegaard 2011]⁶, MEGA study [van Hylckama Vlieg 2009]⁷, German Case-Control study [Dinger 2010]⁸, PharMetrics [Jick 2011]⁹, GPRD study [Parkin 2011]¹⁰)

Although the absolute VTE rates are increased for users of hormonal contraceptives compared to non-users, the rates during pregnancy are even greater, especially during the post-partum period (see Figure 2). The risk of VTE in women using COCs has been estimated to be 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use. Data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.

The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

Figure 2 shows the risk of developing a VTE for women who are not pregnant and do not use oral contraceptives, for women who use oral contraceptives, for pregnant women, and for women in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 2: Likelihood of Developing a VTE



* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

If feasible, stop Yasmin Plus at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Yasmin Plus no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Yasmin Plus if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. [See Adverse Reactions (6).]

5.2 Hyperkalemia

Yasmin Plus contains 3 mg of the progestin DRSP, which 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 (that is, renal impairment, hepatic impairment, and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration should have their serum potassium concentration checked during the first treatment cycle. Medications that may increase serum potassium concentration include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Yasmin Plus because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Yasmin Plus if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Yasmin Plus if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

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. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Yasmin Plus. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Yasmin Plus develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Yasmin Plus if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Data from ten Yasmin contraceptive efficacy clinical trials (N=2,467) show that the percent of women who took Yasmin and experienced unscheduled bleeding decreased over time from 12% at cycle 2 to 6% (cycle 13). A total of 25 subjects out of 3,009 in the Yasmin and Yasmin Plus trials (<1%) discontinued due to bleeding complaints. These are described as metrorrhagia, vaginal hemorrhage, menorrhagia, abnormal withdrawal bleeding, and menometrorrhagia.

The average duration of scheduled bleeding episodes in the majority of subjects (86%-88%) was 4-7 days. Women who use Yasmin Plus may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from Yasmin contraceptive efficacy trials, during cycles 2 -13, 1 - 11% of women per cycle experienced no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect when COCs are taken inadvertently during early pregnancy, particularly in so far as cardiac anomalies and limb-reduction defects are concerned. Discontinue Yasmin Plus if pregnancy is confirmed and initiate a prenatal vitamin containing folate supplementation.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

5.11 Depression

Women with a history of depression should be carefully observed and Yasmin Plus discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs [*see Drug Interactions (7.2)*].

DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

Folates may mask vitamin B12 deficiency.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.4)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Contraception and Folate Supplementation Clinical Trials

The data provided reflect the experience with the use of Yasmin (3 mg DRSP/0.03 mg EE) in the adequate and well-controlled studies for contraception (N=2,837) and folate supplementation (N=172). For contraception, the US pivotal clinical study (N=326) for the oral contraception indication for Yasmin was a multicenter, open-label trial in healthy women aged 18-35 who were treated with Yasmin for up to 13 cycles. The second contraceptive pivotal study (N=442) was a multicenter, randomized, open-label comparative European study of Yasmin vs. 0.150 mg desogestrel/0.03 mg EE conducted in healthy women aged 17-40 who were treated for up to 26 cycles. The primary efficacy study using Yasmin Plus for folate supplementation was a randomized, single-center European trial in 172 healthy, female subjects aged 18-40 years comparing the pharmacodynamic effects of Yasmin + 0.451 mg levomefolate calcium to Yasmin co-administered with folic acid during 24 weeks of treatment followed by 20 weeks of open-label Yasmin.

The adverse reactions seen across the 2 indications overlapped and are reported using the frequencies from the pooled dataset. The most common adverse reactions ($\geq 2\%$ of users) were: premenstrual syndrome (12.4%), headache/migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%), mood changes (depression, depressed mood, irritability, mood swings, mood altered and affect lability (2.3%), and abdominal pain/discomfort/tenderness (2.2%).

Adverse Reactions ($\geq 1\%$) Leading to Study Discontinuation

Contraception Clinical Trials

Of 2,837 women, 6.7% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was headache/migraine (1.5%).

Folate Clinical Trial

There were no subjects who discontinued due to an adverse reaction.

Serious Adverse Reactions:

Contraception Clinical Trials: depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma.

Folate Supplementation Clinical Trial: none reported in the clinical trial

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Yasmin. 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.

Adverse reactions, including fatalities, are grouped into System Organ Classes and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, intracardiac thrombosis, intracranial venous sinus thrombosis, sagittal sinus thrombosis, retinal vein occlusion, myocardial infarction and stroke), hypertension

Hepatobiliary disorders: Gallbladder disease

Immune system disorders: Hypersensitivity

Metabolism and nutrition disorders: Hyperkalemia

Skin and subcutaneous tissue disorders: Chloasma

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St.

John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin with certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the CYP system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Yasmin Plus with other drugs that may increase serum potassium concentration [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

7.3 Effects of Folates on Other Drugs

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

7.4 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate concentrations by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

7.5 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity. Folates may mask vitamin B12 deficiency. [See *Warnings and Precautions* (5.12) and *Drug Interactions* (7.2).]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE tablets (Yasmin), about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Studies to date indicate there is no adverse effect of folate on nursing infants.

8.4 Pediatric Use

Safety and efficacy of Yasmin Plus has been established in women of reproductive age. Efficacy is 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.

8.5 Geriatric Use

Yasmin Plus has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Yasmin Plus is contraindicated in patients with renal impairment [*see Contraindications (4) and Warnings and Precautions (5.2)*].

In subjects with creatinine clearance (CL_{cr}) of 50–79 mL/min, serum DRSP concentrations were comparable to those in a control group with CL_{cr} ≥ 80 mL/min. In subjects with CL_{cr} of 30–49 mL/min, serum DRSP concentrations were on average 37% higher than those in the control group. In addition, there is a potential to develop hyperkalemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium-sparing drugs [*see Clinical Pharmacology (12.3)*].

8.7 Patients with Hepatic Impairment

Yasmin Plus is contraindicated in patients with hepatic disease [*see Contraindications (4) and Warnings and Precautions (5.4)*]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Yasmin Plus has not been studied in women with severe hepatic impairment.

8.8 Race

No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP 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.

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.

11 DESCRIPTION

Yasmin Plus (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) provides an oral contraceptive regimen consisting of 28 film-coated tablets that contain the active ingredients specified for each tablet below:

- 21 orange tablets each containing 3 mg DRSP, 0.03 mg EE as betadex clathrate, and 0.451 mg levomefolate calcium
- 7 light orange tablets each containing 0.451 mg levomefolate calcium

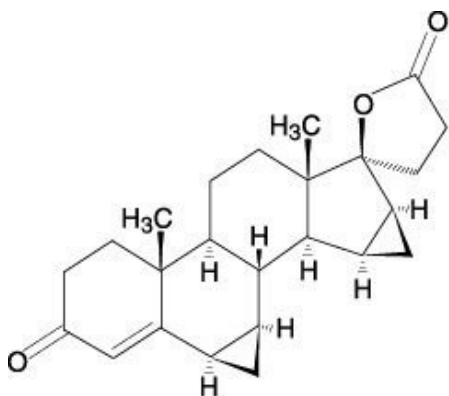
The inactive ingredients in the orange tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose 5 cP, magnesium stearate, hypromellose 5cP, titanium dioxide, talc, macrogol 6000, ferric oxide, yellow, and ferric oxide, red. The light orange film-coated tablets contain 0.451 mg of levomefolate calcium. The inactive ingredients in the light orange tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose 5 cP, magnesium stearate, hypromellose 5cP, titanium dioxide, talc, macrogol 6000 and ferric oxide, yellow, and ferric oxide, red.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13, 14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-[6,7:15,16] cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

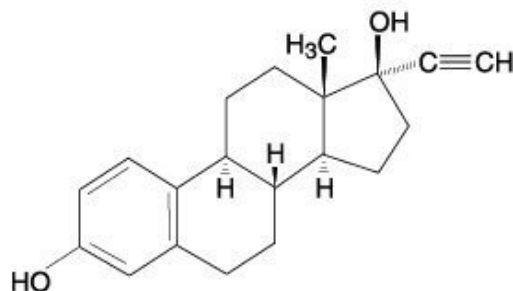
Ethinyl estradiol (19-nor-17 α -pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

Levomefolate calcium (N-[4-[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridiny]methyl]amino]benzoyl]-L-glutamic acid, calcium salt) is a synthetic calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF), which is a metabolite of vitamin B₉ and has a molecular weight of 497.5 and a molecular formula of $C_{20}H_{23}CaN_7O_6$.

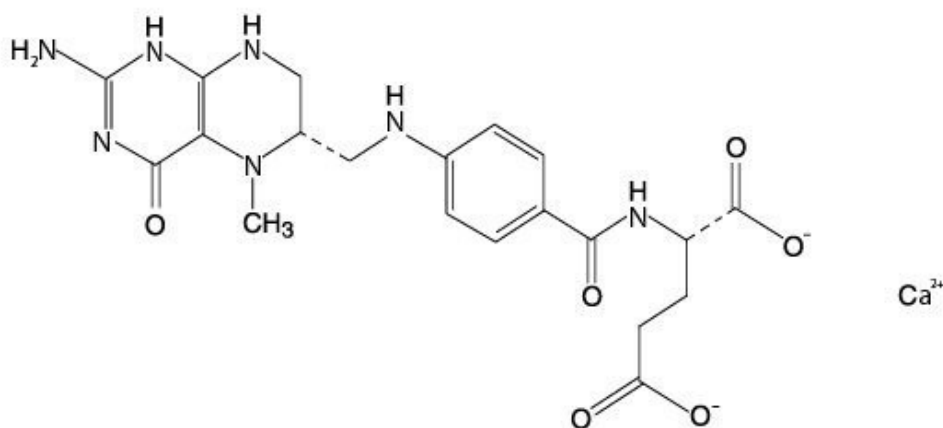
The structural formulas are as follows:



Drospirenone



Ethinyl estradiol



Levomefolate Calcium

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

Drospirenone is a spiroinolactone analogue with antimineralocorticoid activity. The estrogen in Yasmin Plus is ethinyl estradiol (EE).

Contraception

No specific pharmacodynamic studies were conducted with Yasmin Plus.

Folate Supplementation

Two studies evaluated the impact of Yasmin Plus on plasma folate and red blood cell (RBC) folate levels. A randomized, double-blind, active-controlled, parallel group study compared plasma folate and RBC folate levels during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ) + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population. The pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). [See *Clinical Studies* (14.4).]

12.3 Pharmacokinetics

Absorption

Yasmin Plus and Yasmin are bioequivalent with respect to DRSP and EE.

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

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

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of Yasmin serum C_{max} and AUC (0-24h) values of EE accumulate by a factor of about 1.5 to 2 (see Table 2).

Levomefolate calcium is structurally identical to L-5-methyltetrahydrofolate (L-5-methyl-THF), a metabolite of vitamin B₉. 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 and is incorporated into the body folate pool. Peak plasma concentrations of about 50 nmol/L above baseline are reached within 0.5 – 1.5 hours after single oral administration of 0.451 mg levomefolate calcium.

Steady state conditions for total folate 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.

Table 2: Mean Pharmacokinetic Parameters Of YASMIN**(DRSP 3 mg and EE 0.03 mg)**

DRSP Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	AUC(0-24h) (ng•h/mL)	t_{1/2} (h)
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)
EE Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (pg/mL)	T_{max} (h)	AUC(0-24h) (pg•h/mL)	t_{1/2} (h)
1/1	11	53.5 (43)	1.9 (45)	280 (87)	NA
1/21	11	92.1 (35)	1.5 (40)	461 (94)	NA
6/21	11	99.1 (45)	1.5 (47)	346 (74)	NA
9/21	11	87 (43)	1.5 (42)	485 (92)	NA
13/21	10	90.5 (45)	1.6 (38)	469 (83)	NA

NA – Not available

Food Effect

The rate of absorption of DRSP and EE following single administration of a formulation similar to Yasmin Plus was slower under fed (high fat meal) 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 concentrations 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 concentrations). EE is reported to be highly but non-specifically 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.

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. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by CYP3A4.

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and 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 concentrations 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 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% 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.

Use in Specific Populations

Pediatric Use: Safety and efficacy of Yasmin Plus has been established in women of reproductive age. Efficacy is 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.

Geriatric Use: Yasmin Plus has not been studied in postmenopausal women and is not indicated in this population.

Race: No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25-35) when 3 mg DRSP/0.02 mg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

Renal Impairment: Yasmin Plus is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium concentrations were investigated in three separate groups of female subjects (n=28, age 30-65). All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium-sparing drugs for the treatment of their underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP concentrations in the group with CLcr of 50–79 mL/min were comparable to those in the control group with CLcr \geq 80 mL/min. The serum DRSP concentrations were on average 37% higher in the group with CLcr of 30–49 mL/min compared to those in the control group. 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 concentrations increased by up to 0.33 mEq/L. [See *Contraindications* (4) and *Warnings and Precautions* (5.2).]

Hepatic Impairment: Yasmin Plus is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Yasmin Plus has not been studied in women with severe hepatic impairment. [See *Contraindications (4)* and *Warnings and Precautions (5.4)*.]

Drug Interactions

Consult the labeling of all concurrently used drugs to obtain further information about interactions with oral contraceptives or the potential for enzyme alterations.

Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin with certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

Metabolism of DRSP and potential effects of DRSP on hepatic CYP enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*.

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.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Interactions With Drugs That Have the Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Yasmin Plus with other drugs that may increase serum potassium concentration [see *Warnings and Precautions (5.2)*].

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 concentrations were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium concentrations 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 time points 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, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations > 5.5 mEq/L).

Effects of Folates on Other Drugs

There is a potential that folates such as folic acid and levomefolate calcium may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs (e.g., antiepileptics, methotrexate).

Effects of other Drugs on Folate

Several drugs (e.g., methotrexate, sulfasalazine, cholestyramine, antiepileptics) have been reported to reduce folate concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted *in vitro* and *in vivo* and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trial

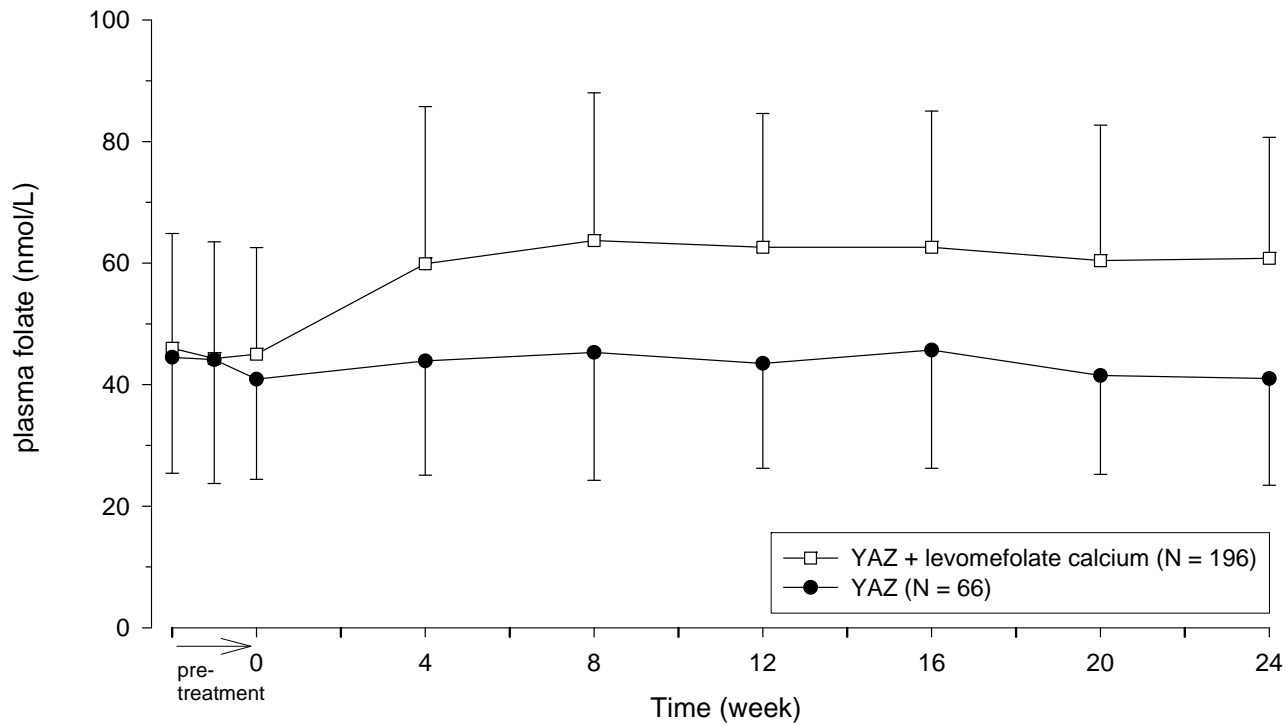
In the clinical efficacy studies of Yasmin (3 mg DRSP/0.03 mg EE) of up to 2 years duration, 2,629 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83% Caucasian, 1% Hispanic, 1% Black, <1% Asian, <1% other, <1% missing data, 14% not inquired and <1% unspecified. Pregnancy rates in the clinical trials were less than one per 100 woman-years of use.

14.2 Folate Supplementation Clinical Trials

The development program for Yasmin Plus (Yasmin + levomefolate calcium) consisted of two clinical trials.

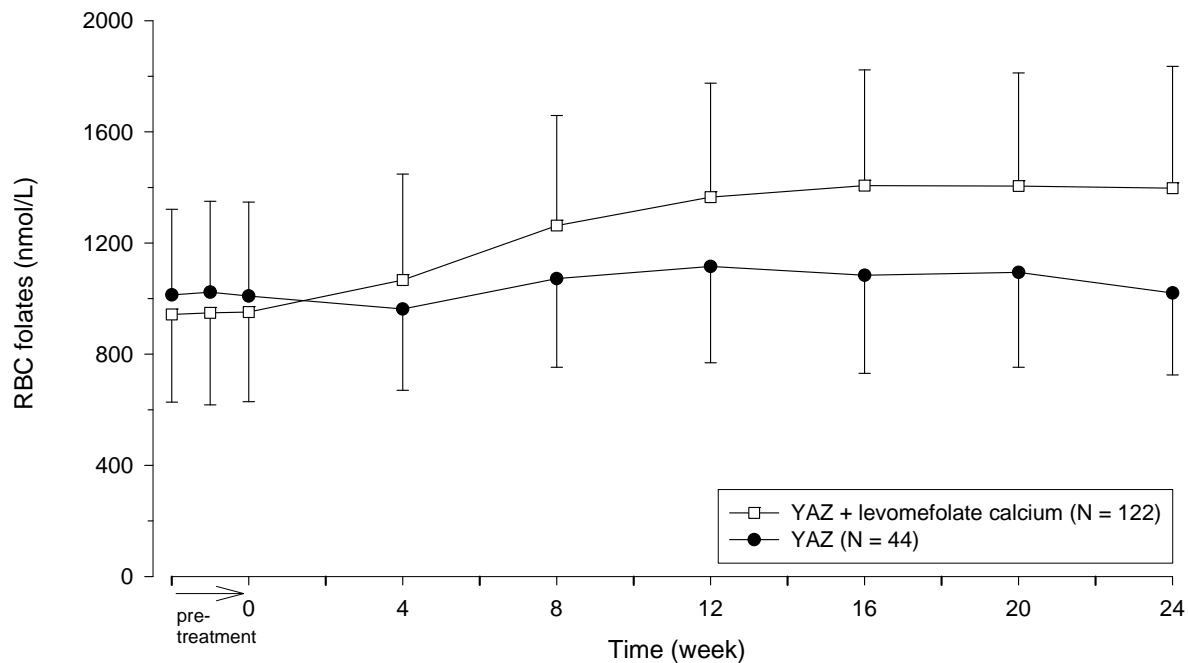
One study was a multicenter, randomized, double-blind, active-controlled, parallel group US study. Plasma folate and red blood cell folate levels were investigated during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ) + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population that consumed folate fortified food. A total of 379 healthy women between 18 and 40 years of age with no restrictions on folate supplementation received YAZ + levomefolate calcium (N= 285) or YAZ (N=94). The plasma and RBC folate concentrations at Week 24 were the co-primary endpoints. Figures 1 and 2 display the results for plasma and RBC folate concentrations, respectively, among evaluable subjects in each arm of the study.

Figure 3: US Study: Mean trough concentration-time curves (and SD) of plasma folates after daily oral administration of YAZ + levomefolate calcium and YAZ



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

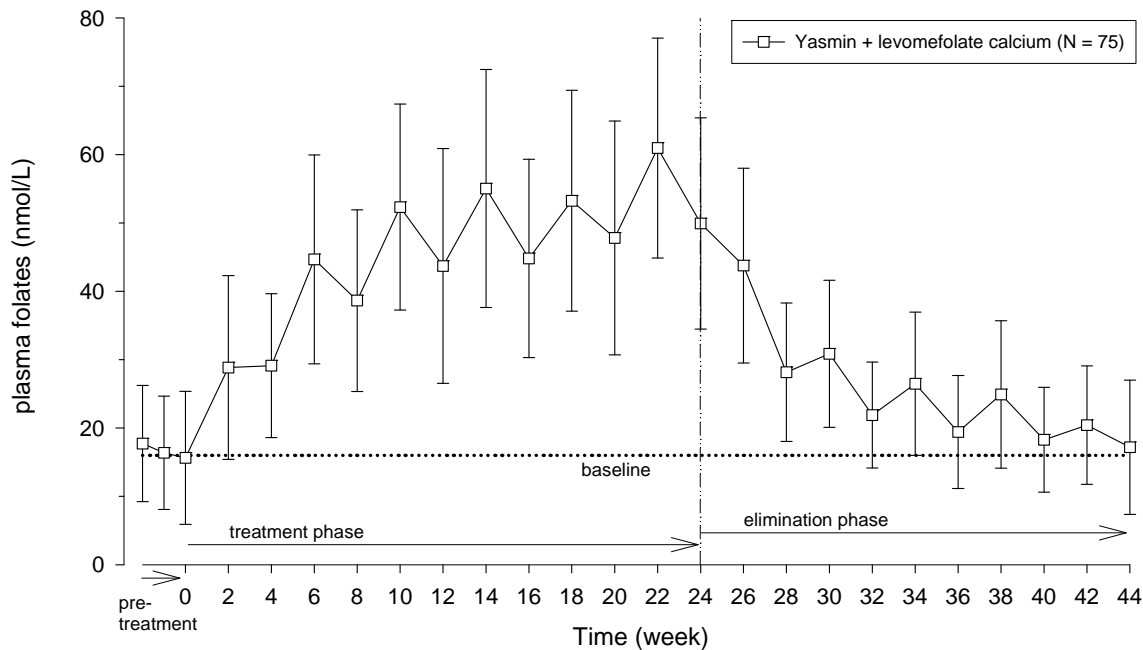
Figure 4: US Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of YAZ + levomefolate calcium and YAZ



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

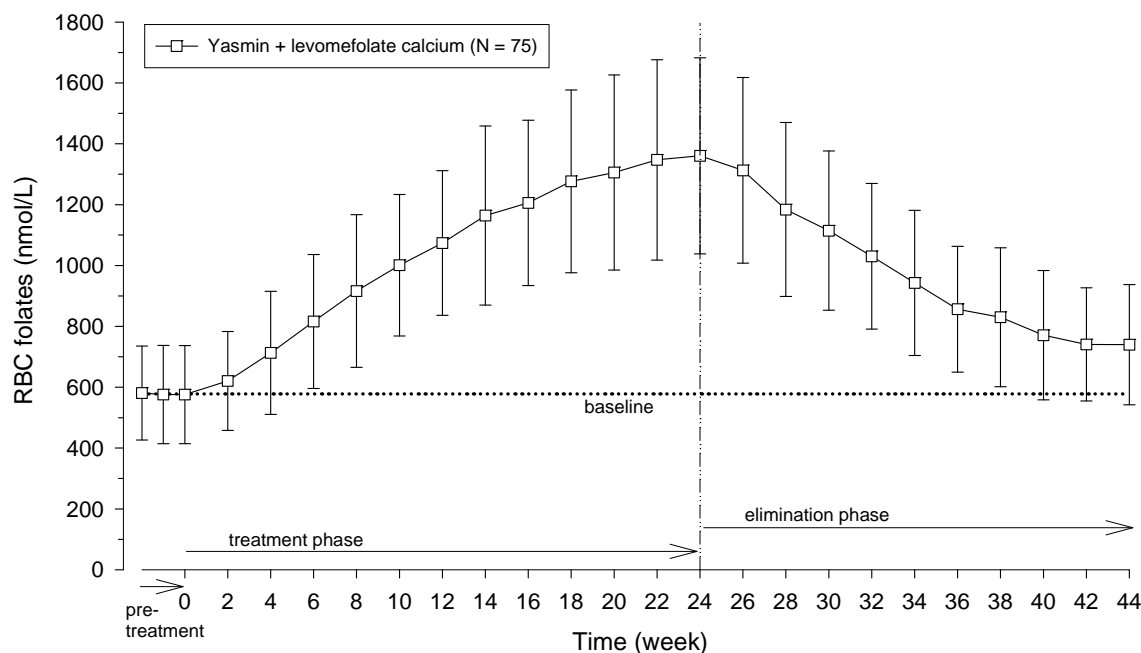
In the second study, the pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). One-hundred and seventy-two healthy women between 18 to 40 years of age from a German population that consumed food without folate fortification and without concomitant intake of folate supplements were randomized to one of the two treatments. Figures 3 and 4 display the results for plasma and RBC folate concentrations, respectively, among evaluable subjects in the levomefolate arm of the study.

Figure 5: German Study: Mean trough concentration-time curve (and SD) of plasma folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on the per protocol analysis population. The SD bars shown represent one SD.

Figure 6: German Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on the per protocol analysis population. The SD bars shown represent one SD.

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, nonrandomized intervention trials, and observational studies using folic acid. Therefore, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily^{1,6}.

15 REFERENCES

1. US Preventive Services Task Force. Folic Acid for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2009;150:626-631.
2. Seeger, J.D., Loughlin, J., Eng, P.M., Clifford, C.R., Cutone, J., and Walker, A.M. (2007). Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 110, 587-593.
3. Dinger, J.C., Heinemann, L.A., and Kuhl-Habich, D. (2007). The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 75, 344-354.
4. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney, S. (primary author) <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf>, accessed Oct 27, 2011.
5. Lidegaard, O., Lokkegaard, E., Svendsen, A.L., and Agger, C. (2009). Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 339, b2890.
6. Lidegaard, O., Nielsen, L.H., Skovlund, C.W., Skjeldestad, F.E., and Lokkegaard, E. (2011). Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ* 343, d6423.

7. van Hylckama Vlieg, A., Helmerhorst, F.M., Vandenbroucke, J.P., Doggen, C.J., and Rosendaal, F.R. (2009). The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 339, b2921.
8. Dinger, J., Assmann, A., Mohner, S., and Minh, T.D. (2010). Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care* 36, 123-129.
9. Jick, S.S., and Hernandez, R.K. (2011). Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 342, d2151.
10. Parkin, L., Sharples, K., Hernandez, R.K., and Jick, S.S. (2011). Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 342, d2139.
11. Centers for Disease Control. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR* 1992;41(No. RR-14).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Yasmin Plus (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in packages of three blister packs (NDC 50419-403-03).

The film-coated tablets are rounded with biconvex faces, one side is embossed with a regular hexagon shape with Y+ or M+.

Each blister pack contains 28 film-coated tablets in the following order:

- 21 round, biconvex, orange, film-coated tablets with embossed “Y+” in a regular hexagon on one side each containing 3 mg drospirenone, 0.03 mg ethinyl estradiol, and 0.451 mg levomefolate calcium
- 7 round, biconvex, light orange, film-coated tablets with embossed “M+” in a regular hexagon on one side each containing 0.451 mg levomefolate calcium

16.2 Storage

Do not store above 25°C

MANUFACTURER: Bayer Pharma AG, Berlin, Germany.

REGISTRATION HOLDER: Bayer Israel Ltd, 36 Hacharash St., Hod Hasharon 45240.