

Revised: June 2015
Rx Only
Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets, 3 mg/0.03 mg/0.451 mg and Levomefolate Calcium Tablets, 0.451 mg

FPO

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets safely and effectively. See full prescribing information for drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets.

DROSPIRENONE, ETHINYL ESTRADIOL, and LEVOMEFOLATE calcium tablets and LEVOMEFOLATE calcium tablets, for oral use
Initial U.S. Approval: 2010

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning

- Women over 35 years old who smoke should not use drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets. (4)
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)

-----RECENT MAJOR CHANGES-----
Warnings and Precautions, Hyperkalemia (5.2) 5/2015

-----INDICATIONS AND USAGE-----
Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are an estrogen/progestin COC containing a folate, indicated for use by women to:

- Prevent pregnancy. (1,1)
- Raise folate levels in women who choose to use an oral contraceptive for contraception. (1,2)

-----DOSAGE AND ADMINISTRATION-----
• Take one tablet daily by mouth at the same time every day. (2.1)
• Tablets must be taken in the order directed on the blister pack. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----
Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets consist of 28 film-coated, bi-convex tablets in the following order (3):

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

-----CONTRAINDICATIONS-----
• Renal impairment (4)
• Adrenal insufficiency (4)
• A high risk of arterial or venous thrombotic diseases (4)
• Undiagnosed abnormal uterine bleeding (4)
• Breast cancer or other estrogen- or progestin-sensitive cancer (4)
• Liver tumors or liver disease (4)
• Pregnancy (4)

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FULL PRESCRIBING INFORMATION
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
Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are indicated for use by women to prevent pregnancy.

1.2 Folate Supplementation
Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are 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 Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets
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, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets
Instruct the patient to begin taking drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablet use, instruct the patient to take one orange drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablet daily, beginning on Day 1 of her menstrual cycle. (The first day of menstruation is Day 1.) She should take one orange drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablet daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on Days 22 through 28. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets can be taken without regard to meals. If drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are first taken later than the first day of the menstrual cycle, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets use, instruct the patient to take one orange drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablet daily, beginning on the first Sunday after the onset of her menstrual period. She should take one orange drospirenone, ethinyl estradiol and levomefolate calcium tablet daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on Days 22 through 28. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets can be taken without regard to meals. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets daily for seven consecutive days.

When switching from a different birth control pill
When switching from another birth control pill, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets should be started when the next application would have been due. When switching from an injection, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets, instruct the patient to continue taking drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 to 4 hours after tablet-taking, this can be regarded as a missed tablet.

-----WARNINGS AND PRECAUTIONS-----

- **Vascular risks:** Stop drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if a thrombotic event occurs. Start on or after at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery. In women who are not breastfeeding, (5.1) COCs containing DRSP may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing levonorgestrel or some other progestins. Before initiating drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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. (5.1)
- **Hyperkalemia:** DRSP has anti-mineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium concentration during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium concentration. (5.2, 7.1, 7.2)
- **Liver disease:** Discontinue drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if jaundice occurs. (5.4)
- **High blood pressure:** Do not prescribe drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- **Carbohydrate and lipid metabolic effects:** Monitor pre-diabetic and diabetic women taking drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- **Headache:** Evaluate significant change in headaches and discontinue drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if indicated. (5.8)
- **Uterine bleeding:** Evaluate irregular bleeding or amenorrhea. (5.9)

-----ADVERSE REACTIONS-----

The most frequent adverse reactions (greater than or equal to 2%) in contraception and folate clinical trials are premenstrual syndrome (12.4%), headache/migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%), mood changes (2.3%) and abdominal pain/tenderness/discomfort (2.2%), (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-272-5525 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----DRUG INTERACTIONS-----

Drugs or herbal products that induce certain enzymes (for example, CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

-----USE IN SPECIFIC POPULATIONS-----

Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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7 DRUG INTERACTIONS

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*Sections or subsections omitted from the full prescribing information are not listed

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. Consider other folate supplementation that a woman may be taking before prescribing drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets. Ensure that folate supplementation is maintained if a woman discontinues drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets due to pregnancy.

3 DOSAGE FORMS AND STRENGTHS
Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are 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 debossed with "W" on one side and "265" on the other side.
- 7 light orange tablets each containing 0.451 mg levomefolate calcium debossed with "W" on one side and "297" on the other side.

4 CONTRAINDICATIONS

Do not prescribe drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 have had a stroke or malignant or liver disease [see Warnings and Precautions (5.1)]
 - o Smoke, if over age 35 [see Boxed Warning and Warnings and Precautions (5.1)]
 - o Have deep vein thrombosis or pulmonary embolism, now or in the past [see Warnings and Precautions (5.1)]
 - o Have cerebrovascular disease [see Warnings and Precautions (5.1)]
 - o Have coronary artery disease [see Warnings and Precautions (5.1)]
 - o Have thrombotic valvular or thrombotic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see Warnings and Precautions (5.1)]
 - o Have inherited or acquired hypercoagulopathies [see Warnings and Precautions (5.1)]
 - o Have uncontrolled hypertension [see Warnings and Precautions (5.5)]
 - o Have diabetes mellitus with vascular disease [see Warnings and Precautions (5.7)]
 - o Have headaches with focal neurological symptoms or have migraine with aura, 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 disease, including acute or chronic 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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. Know your risks for VTE include smoking, obesity, and family history of VTE. In addition to other factors that contraindicate use of COCs [see Contraindications (4)].

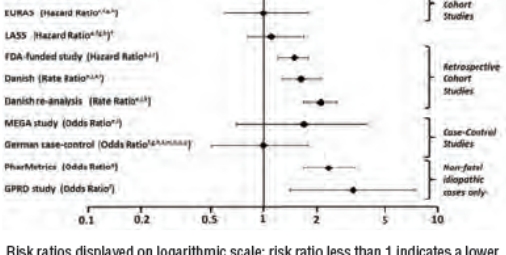
A number of studies have compared the risk of VTE for users of Yasmin[®] (which contains 0.03 mg of EE and 3 mg of DRSP) to the risk for users of other COCs, including COCs containing levonorgestrel. Those that were required or sponsored by regulatory agencies are summarized in Table 1.

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

Epistemiologic 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)
IG (biggest) (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 ^b	HR: 0.9 (0.6-1.4)
"FDA-funded study" (2011) New users ^c	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)
All users (i.e., initiation and continuing use of study combination hormonal contraception)	Other COCs available during the course of the study ^d	HR: 1.7 (1.4-2.1)
	Levonorgestrel/0.03 mg EE	HR: 1.5 (1.2-1.8)

a) "New users" = 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)^a



^aComparator "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

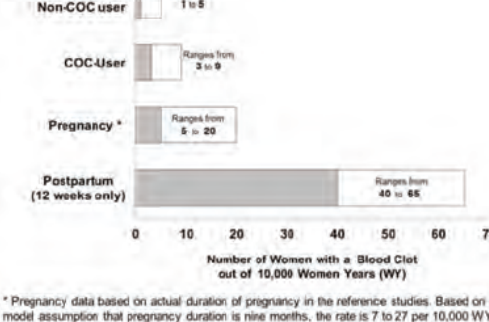
(References: Ingenix [Seeger 2007]², EURAS [European Active Surveillance Study] [Dinger 2007]³, LASS [Long-Term Active Surveillance Study] [Dinger, unpublished document in file], FDA-funded study [Sidney 2011]⁴, Danish [Lidegaard 2009]⁵, Danish re-analysis [Lidegaard 2011]⁶, MEGA study [van Hylckama 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 10 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 starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.

The risk of the 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 (greater than 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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

Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets contain 3 mg of the progestin DRSP, which has anti-mineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are contraindicated 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. Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly. Strong CYP3A4 inhibitors include azole antifungals (e.g., ketoconazole, itraconazole, voriconazole), HIV protease inhibitors (e.g., indinavir, boceprevir), and clarithromycin [see Clinical Pharmacology (12.3)].

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbance of liver function may

10 OVERDOSEAGE

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

DRSP is a spironolactone analogue which has anti-mineralocorticoid 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets) were well tolerated after long-term treatment up to 12 weeks.

11 DESCRIPTION

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

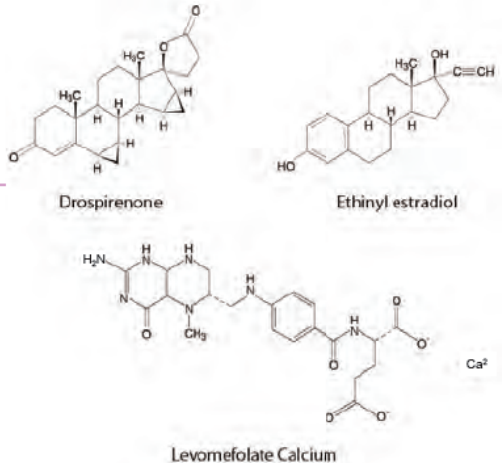
The inactive ingredients in the orange tablets are lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, titanium dioxide, hypromellose, polyethylene glycol, vitamin E, FD&C Yellow No. 6/Sunset Yellow FCF aluminum lake, FD&C Red No. 40/Allura Red AC aluminum lake, and polysorbate 80. The inactive ingredients in the light orange tablets are lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, FD&C Yellow No. 6/Sunset Yellow FCF aluminum lake, polysorbate 80, and FD&C Red No. 40/Allura Red AC aluminum lake.

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-dicyclopenta[6,7:15,16]cyclopenta[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 C₂₄H₃₄O₅.

Ethinyl estradiol (19-nor-17 α -pregna-1,3,5(10)-trien-20-yn-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of C₂₀H₂₄O₂.

Levomefolate calcium [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] 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 C₂₀H₂₃CaN₄O₆.

The structural formulas are as follows:



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 spironolactone analogue with antiminerocorticoid activity. The estrogen in drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets is ethinyl estradiol (EE).

Contraception

No specific pharmacodynamic studies were conducted with drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets.

Folate Supplementation

Two studies evaluated the impact of drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 (14.2)].

12.3 Pharmacokinetics

Absorption

Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets, 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 to 2 hours after administration of drospirenone, ethinyl estradiol and levomefolate calcium tablets.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1 to 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 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 to 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 to 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)

Cycle / Day	No. of Subjects	DRSP Mean (%CV) Values			
		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)
Cycle / Day	No. of Subjects	EE Mean (%CV) Values			
		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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 to 5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough concentrations). EE is reported to be highly but not 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 to 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, formed by reduction and subsequent sulfatation. These metabolites were shown not to be pharmacologically active. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.

EE has been reported to be subject to significant gut and hepatic first-pass metabolism. Metabolism of EE and its oxidative metabolites occur primarily by conjugation with glucuronide 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 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 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.

Use in Specific Populations

Pediatric Use: Safety and efficacy of drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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: Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 to 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: Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are 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 to 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 CL_{cr} of 50 to 79 mL/min were comparable to those in the control group with CL_{cr} greater than or equal to 80 mL/min. The serum DRSP concentrations were on average 37% higher in the group with CL_{cr} of 30 to 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: Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are 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. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets have 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: Coadministration 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. In a clinical drug-drug interaction study conducted in 20 premenopausal women, coadministration of a DRSP (3 mg)/EE (0.02 mg) COC with the strong CYP3A4 inhibitor ketoconazole (200 mg twice daily) for 10 days increased the AUC(0-24h) of DRSP and EE by 2.68-fold (90% CI: 2.44, 2.95) and 1.40-fold (90% CI: 1.31, 1.49), respectively. The increases in C_{max} were 1.97-fold (90% CI: 1.79, 2.17) and 1.39-fold (90% CI: 1.28, 1.52) for DRSP and EE, respectively. Although no clinically relevant effects on safety or laboratory parameters including serum potassium were observed in this study, only women with normal renal function were included in a patient taking a DRSP-containing COC concomitantly with chronic use of a CYP3A4 inhibitor is unknown [see Warnings and Precautions (5.2)].

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 coadministration 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 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, EE is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism-based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. 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 effect 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 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets 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 0.85 (90% CI: 0.814, 0.889) and 1.010 (90% CI: 0.844, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations greater than 5.5 mEq/L).

Effects of Foliates 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 hardier 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 3 + 0.03, 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 mutagenicity 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 mutagenicity was observed.

14 CLINICAL STUDIES

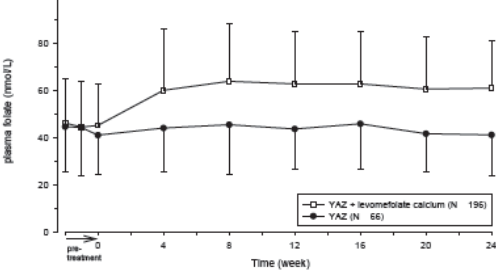
14.1 Oral Contraceptive Clinical Trial
In the clinical efficacy studies of Yasmin[®] (3 mg DRSP/0.03 mg EE) of up to 2 years duration, 2,029 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83% Caucasian, 1% Hispanic, 1% Black, less than 1% Asian, less than 1% other, less than 1% missing data, 14% not inquired and less than 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 drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets (Yasmin[®] + levomefolate calcium) consisted of two clinical trials.

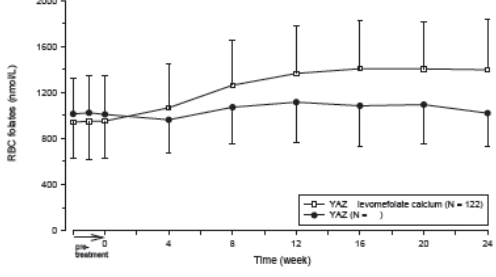
One study was a multicenter, randomized, double-blind, active-controlled, parallel group US study. Plasma folate and red blood cell folate levels were investigated during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ[®]) + 0.451 mg levomefolate calcium as compared to YAZ[®] alone in a U.S. population 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 3 and 4 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[®].

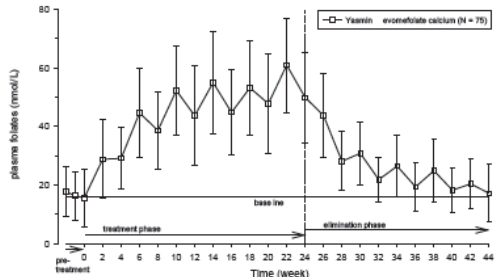


Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on the per protocol analysis populations. The SD bars shown represent one SD.

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

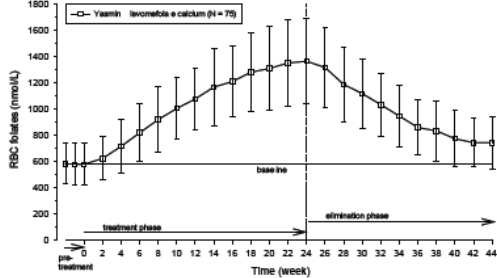
treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin[®]) followed by 20 weeks of open-label treatment with Yasmin[®] only (elimination phase). One-hundred and seventy-two healthy 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 5 and 6 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.¹⁸

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GLUE PANEL
Hot Melt
Non Fiber Tearing

LABEL
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Drospirenone Ethinyl Estradiol and Levomefolate Calcium Tablets, 3 mg/0.03 mg/0.451 mg and Levomefolate Calcium Tablets, 0.451 mg

Rx Only
Revised: June 2015



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Drospirenone Ethinyl Estradiol and Levomefolate Calcium Tablets, 3 mg/0.03 mg/0.451 mg and Levomefolate Calcium Tablets, 0.451 mg

Pick the day label that starts with the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when the bleeding begins). Place the strip on the blister card over the words "PLACE ENCLOSED DAY LABEL HERE". Each day will line up with a row of pills.

It is important to take your pill every day. If you missed a pill, please refer to the FDA-Approved Patient Labeling or contact us at 1-800-272-5525.

Healthcare Provider's Phone #: _____

Watson Laboratories, Inc.
Corona, CA 92880 USA

FDA Approved Patient Labeling Guide for Using Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets

WARNING TO WOMEN WHO SMOKE

Do not use drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What are Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets?

Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets also contains levomefolate calcium, which is a B vitamin.

The progestin drospirenone may increase potassium. Therefore, you should not take drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets are right for you, and during the first month that you take drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin*, Advil*], naproxen [Aleve* and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten*, Vasotec*, Zestril* and others)
- Angiotensin-II receptor antagonists (Cozaar*, Diovan*, Avapro* and others)
- Heparin
- Aldosterone antagonists

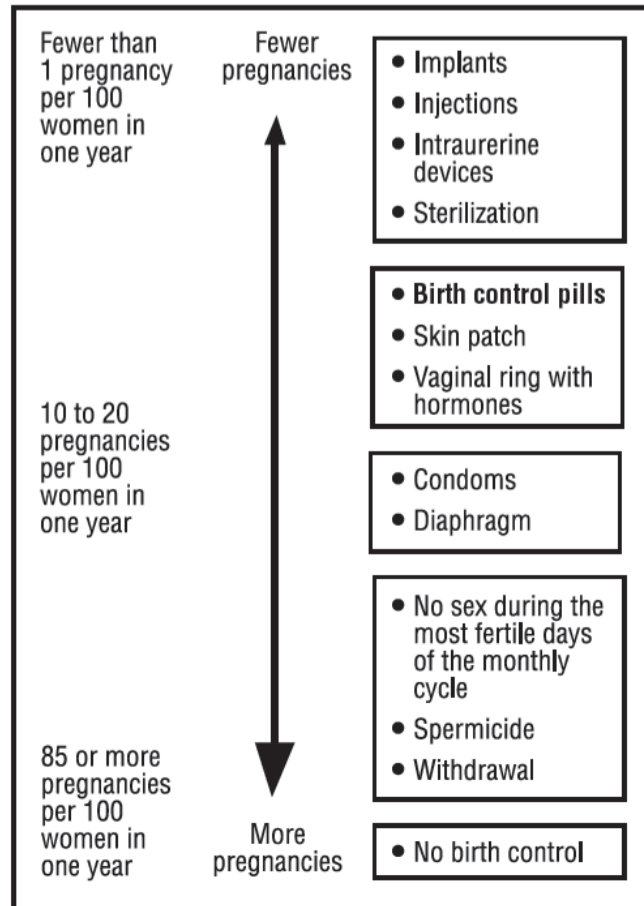
Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets may also be taken by women who elect to use an oral contraceptive, to provide folate supplementation. It is recommended that women of reproductive age supplement their diet with 0.4 mg (400 mcg) of folic acid daily to lower their risk of having a pregnancy with a rare type of birth defect (known as a neural tube defect). The amount of folate contained in drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets supplements folate in the diet to lower this risk should you become pregnant while taking the drug or shortly after stopping it.

How Well Do Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of two clinical studies, about 1 woman out of 100 women may get pregnant during the first year they use drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Do I Take Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets?

1. Be sure to read these directions before you start taking your pills or anytime you are not sure what to do.
2. The right way to take the pill is to take one pill every day at the same time in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets can be taken without regard to meals.
3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1 to 3 packs of pills.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. Missing pills can also cause spotting or light bleeding, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.

6. If you have trouble remembering to take the pill, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

7. If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

Before You Start Taking Your Pills

1. Decide What Time of Day You Want to Take Your Pill

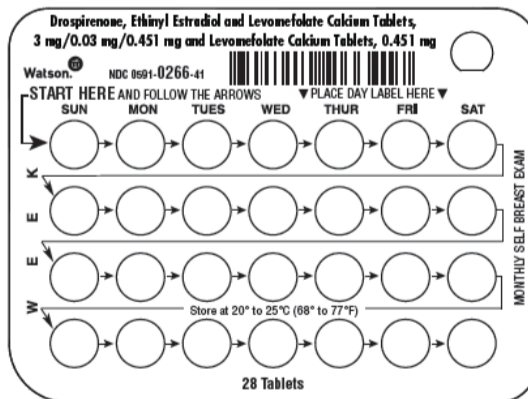
It is important to take drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets can be taken without regard to meals.

2. Look at Your Pill Pack - It has 28 Pills

The drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablet pill pack has 21 orange pills (with hormones and folate) to be taken for three weeks, followed by 7 light orange pills (without hormones, containing folate) to be taken for one week. It is important to take the light orange pills because they contain folate.

3. Also look for:

- a) Where on the pack to start taking pills,
- b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms and spermicides) to use as a back-up in case you miss pills, and (b) an extra, full pill pack.

When To Start the First Pack of Pills

You have a choice for which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

Day 1 Start:

1. Take the first orange pill of the pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, because you are starting the Pill at the beginning of your period. However, if you start drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 orange pills.

Sunday Start:

1. Take the first orange pill of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first

pack until the next Sunday (7 days). This also applies if you start drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets after having been pregnant and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Pill

When switching from another birth control pill, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets should be started on the same day that a new pack of the previous birth control pill would have been started.

When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets should be started when the next application would have been due. When switching from an injection, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets should be started on the day of removal.

What to Do During the Month

1. Take one pill at the same time every day until the pack is empty.

Do not skip pills even if you are spotting or 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 of pills, start the next pack on the day after your last light orange pill. It is important to take the light orange pills because they contain folate. Do not wait any days between packs.

What to Do if You Miss Pills

If you miss 1 orange pill of your pack:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.

2. You do not need to use a back-up birth control method if you have sex.

If you miss 2 orange pills in a row in Week 1 or Week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

If you miss 2 orange pills in a row in Week 3 of your pack:

1. If you are a Day 1 Starter:
Throw out the rest of the pill pack and start a new pack that same day.
2. If you are a Sunday Starter:
Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.
3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

4. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.

If you miss 3 or more orange pills in a row during any week:

1. If you are a Day 1 Starter:
Throw out the rest of the pill pack and start a new pack that same day.
2. If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.
3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms and spermicides) as a back-up for those 7 days.

4. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.

If you miss any of the 7 light orange pills in Week 4:

1. Throw away the pills you missed.
Keep taking one pill each day until the pack is empty.
2. You do not need a back-up method.

Finally, if you are still not sure what to do about the pills you have missed:

Use a back-up method (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active orange pill each day until otherwise directed.

WHO SHOULD NOT TAKE DROSPIRENONE, ETHINYL ESTRADIOL AND LEVOMEFOLATE CALCIUM TABLETS AND LEVOMEFOLATE CALCIUM TABLETS?
Your healthcare provider will not give you drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if you:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- Have an inherited problem with your blood that makes it clot more than normal
- Have high blood pressure that medicine can't control
- Have diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Have liver disease, including liver tumors
- Have kidney disease
- Have adrenal disease

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

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

Tell your healthcare provider if you are already taking daily folate supplements.

What Else Should I Know about Taking Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets?
Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills on time every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

Due to an increased risk of blood clots, you should stop drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

Folates may make certain drugs, including some used for epilepsy, less effective, so talk to your healthcare provider about any medicines you take.

If you have vomiting or diarrhea, your birth control pills may not work as well. Take another pill if you vomit within 3-4 hours after taking your pill, or use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Yasmin* may affect the way other medicines work, and other medicines may affect how well Yasmin* works. Know the medicines you take.

Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more. Women who use birth control pills with drospirenone (like drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets) may have a higher risk of getting a blood clot. Some studies reported that the risk of blood clots was higher for women who use birth control pills that contain drospirenone than for women who use birth control pills that do not contain drospirenone.

Talk with your healthcare provider about your risk of getting a blood clot before deciding which birth control pill is right for you.

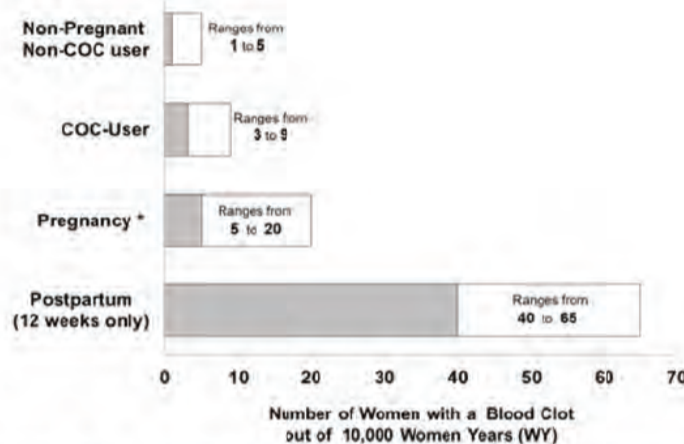
It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (deep vein thrombosis or DVT)
- Lungs (pulmonary embolus or PE)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use birth control pills are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not

pregnant and do not use birth control pills, for women who use birth control pills, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot



* 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.

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets?

Irregular vaginal bleeding or spotting may occur while you are taking drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the pills regularly on time.

What if I Miss My Scheduled Period when Taking Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets?

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills regularly on time, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets if you are pregnant.

What if I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill. See your healthcare provider about appropriate folate supplementation if you stop taking drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets, are pregnant, or plan on becoming pregnant.

General Advice about Drospirenone, Ethinyl Estradiol and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets

Your healthcare provider prescribed drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets for you. Please do not share drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets with anyone else. Keep drospirenone, ethinyl estradiol and levomefolate calcium tablets and levomefolate calcium tablets out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

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