

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it on Feb 2010.

Prescribing Information

YASMIN

1. NAME OF THE MEDICINAL PRODUCT

Yasmin, film-coated tablets, 0.03 mg/3 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 hormone-containing light yellow film-coated tablets:
Each film-coated tablet contains 3 mg drospirenone and 0.03 mg ethinylestradiol.
Excipient: lactose 48.17 mg.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.
The tablet is light yellow, round with convex faces, one side embossed with the letters "DO" in a regular hexagon

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

4.2 Dosage and method of administration

Method of administration

Oral use

Dosage regimen

How to take Yasmin

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

The tablets must be taken in the order directed on the package every day at about the same time, with some liquid as needed.

One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval, during which time a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start Yasmin

- No preceding hormonal contraceptive use (in the past month)
Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.
- Changing from another combined oral contraceptive (combined oral contraceptive /COC, vaginal ring, or transdermal patch)

The woman should start with Yasmin preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Meliane preferably on the day of the removal, but at the latest when the next application would have been due.

- Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill (from an implant on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- Following first-trimester abortion

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

- Following delivery or second-trimester abortion
For breastfeeding women see Section 'Pregnancy and lactation'.

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets

If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection maybe reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

Week 1

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

Week 2

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time.

Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Week 3

The risk of reduced reliability is imminent because of the forthcoming 7-day tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next blister pack must be started as soon as the current blister pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet-taking from the current blister pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets, as given in Section 'Management of missed tablets', is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another pack.

How to shift periods or how to delay a period

To delay a period the woman should continue with another blister pack of Yasmin without a tablet-free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Yasmin is then resumed after the usual 7-day tablet-free interval.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval by as many days as she likes. The shorter the interval the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

Additional information on special populations

Children and adolescents

Yasmin is only indicated after menarche. There are no data suggesting the need for a dosage adjustment.

Geriatric patients

Not applicable. Yasmin is not indicated after menopause.

Patients with hepatic impairment

Yasmin is contraindicated in women with severe hepatic diseases. See also sections 'Contraindications' and 'Pharmacokinetic properties'.

Patients with renal impairment

Yasmin is contraindicated in women with severe renal insufficiency or acute renal failure. See also sections 'Contraindications' and 'Pharmacokinetic properties'.

4.3 Contra-indications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately.

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see under "Special Warnings and Special precautions for Use"):
- History of migraine with focal neurological symptoms.

- Diabetes mellitus with vascular involvement.severe hypertension
- severe dyslipoproteinaemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Severe hepatic disease as long as liver values have not returned to normal.
- Severe renal insufficiency or acute renal failure.
- Presence or history of liver tumors (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and special precautions for use

Warnings

If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued.

- **Circulatory Disorders**

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

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

Data from a large, prospective 3-armed cohort study has shown that the incidence of VTE in women with or without other risk factors for VTE who used ethinylestradiol/drospirenone 0.03 mg/3 mg is in the same range as that for users of levonorgestrel-containing COCs and other COCs (various other COC brands).

VTE may be fatal (in 1-2 % of the cases).

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

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COC.

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

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

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

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

Arterial thromboembolic events may be fatal.

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- age;
 - obesity (body mass index over 30 kg/m^2);
 - a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
 - prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization.
 - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
 - dyslipoproteinemia;
 - hypertension;
 - migraine;
 - valvular heart disease;
- atrial fibrillation;

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis venous thromboembolism.

The increased risk of thromboembolism in the puerperium must be considered (for information on pregnancy and lactation" see Section 'Pregnancy and lactation').

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

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.

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

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

Tumors

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

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

- Other conditions

Potassium excretory capacity may be limited in patients with renal insufficiency. In a clinical study,

drospirenone intake did not show an effect on the serum potassium concentration in patients with mild or moderate renal impairment. A theoretical risk for hyperkalemia can be assumed only for patients with renal impairment whose pretreatment serum potassium is in the upper reference range, and who are additionally using potassium sparing drugs.

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. The antimineralocorticoid effect of drospirenone may counteract ethinylestradiol-induced increases in blood pressure observed in normotensive women using other combined oral contraceptives. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05mg ethinylestradiol). However, diabetic women should be carefully observed, while taking COCs.

Crohn's disease, and ulcerative colitis, have been associated with COC use.

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 whilst taking COCs.

Each film-coated tablet of this medicinal product contains 46 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of COC use, , guided by the contra-indications (section 4.3) and warnings (4.4.1) and

should be repeated periodically. Periodical medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g. missed tablets (Section 'Management of missed tablets'), gastro-intestinal disturbances (Section 'Advice in case of gastro-intestinal disturbances') during tablet taking or concomitant medication (Section 'Interaction with other medicinal products and other forms of interaction').

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicaments on Yasmin Interactions of other drugs (enzyme inducers, some antibiotics) with oral contraceptives may lead to breakthrough bleeding and/or contraceptive failure. Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

Substances diminishing the efficacy of COCs (enzyme-inducers and antibiotics)

- *Enzyme induction (increase of hepatic metabolism):* Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones (e.g. phenytoin,

barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort).

Also HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially increase hepatic metabolism.

- *Antibiotics (interference with enterohepatic circulation):* Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Substances interfering with the metabolism of combined hormonal contraceptives (enzyme inhibitors)

The main metabolites of drospirenone in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

Effects of COCs on other medicaments

Oral contraceptives may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporine) or decrease (e.g. lamotrigine).

Based on in vitro inhibition studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrates, an interaction of drospirenone at doses of 3 mg with the metabolism of other drugs is unlikely.

Other forms of interactions

Serum potassium

There is a theoretical potential for an increase in serum potassium in women taking Yasmin with other drugs that may increase serum potassium levels. Such drugs include angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in studies evaluating the interaction of drospirenone (combined with estradiol) with an ACE inhibitor or indomethacin, no clinically or statistically significant differences in serum potassium concentrations were observed.

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

4.6 Pregnancy and lactation

Pregnancy

Yasmin is not indicated during pregnancy. If pregnancy occurs during treatment with Yasmin further intake should be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

The available data regarding the use of Yasmin during pregnancy are too limited to permit conclusions concerning negative effects of Yasmin on pregnancy, health of the fetus or neonate. No relevant epidemiological data are available yet.

Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

4.8 Undesirable effects

The most serious undesirable effects associated with the use of COCs are listed in Section Special warnings and precautions for use'

Other side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are:

System Organ Class	Common ($\geq 1/100$)	Uncommon ($\geq 1/1000$ and $< 1/100$)	Rare ($< 1/1000$)
Eye disorders			contact lens intolerance
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhea	
Immune system disorders			hypersensitivity
Investigations	weight increased		weight decreased
Metabolism and nutrition disorders		fluid retention	
Nervous system disorders	headache	migrane	
Psychiatric disorders	depressed mood, mood altered	libido decreased	libido increased

Reproductive system and breast disorders	breast pain, breast tenderness	breast hypertrophy	vaginal discharge breast discharge
Skin and subcutaneous tissue disorders		Rash, urticaria	Erythema nodosum, erythema multiforme

The most appropriate MedDRA term (version 7.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

4.9 Overdose

There has not yet been any clinical experience of overdose with Yasmin. On the basis of general experience with combined oral contraceptives, symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations ATC Code: G03AA12

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

A large, prospective 3-armed cohort study has shown that the frequency of VTE diagnosis ranges between 8 to 10 per 10,000 woman years in low estrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users, and ranges between 20 to 30 per 10,000 pregnant women or post partum.

As well as protection against pregnancy, COCs have several positive properties which next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

Drospirenone has beneficial properties in addition to contraception. Drospirenone has antimineralocorticoid activity that can prevent weight gain and other symptoms caused by fluid retention. It counteracts the estrogen-related sodium retention providing for a very good tolerance and has positive effects on the premenstrual syndrome. In combination with ethinylestradiol, drospirenone displays a favorable lipid profile with an increase in HDL. Drospirenone exerts antiandrogenic activity leading to a positive effect on the skin and to a reduction in acne lesions and sebum production. In addition, drospirenone does not counteract the ethinylestradiol-related SHBG increase which is useful for binding and inactivating the endogenous androgens.

Drospirenone is devoid of any androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. This, in combination with the antimineralocorticoid and antiandrogenic properties, gives drospirenone a biochemical and pharmacological profile closely resembling the natural hormone progesterone. Apart from this, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dosed COCs (0.05 mg ethinylestradiol) have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

5.2 Pharmacokinetic properties

Drospirenone

Absorption

Orally administered drospirenone is rapidly and completely absorbed. Peak serum concentrations of approx. 37 ng/ml are reached at about 1-2 hours after ingestion. Bioavailability is about 76 - 85 %. Concomitant ingestion of food has no influence on bioavailability.

Distribution

Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3-5 % of the total serum drug concentrations are present as free steroid, 95-97% are non-specifically bound to albumin.. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The apparent volume of distribution of drospirenone is about 3.7 ± 4.2 l/kg.

Metabolism

Drospirenone is completely metabolized. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, both of which are formed without involvement of the P450 system. Drospirenone is metabolized to a minor extent by cytochrome P450 3A4 based on in vitro data. The clearance rate from serum is about 1.2-1.5 ml/min/kg. When drospirenone was acutely co-administered with ethinylestradiol, no direct interaction was found.

Elimination

Drospirenone levels decrease in two phases. The terminal disposition phase is characterized by a half life of approximately 31h. Drospirenone is not excreted in unchanged form. Its metabolites are excreted at a biliary ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and feces is about 1.7 days.

Steady-State Conditions

Drospirenone pharmacokinetics are not influenced by SHBG levels. Following daily ingestion drug serum levels increase about two- to threefold reaching steady-state conditions during the second half of a treatment cycle.

Special Populations

- *Effect of renal impairment*

Steady-state drospirenone levels in women with mild renal impairment (creatinine clearance CL_{cr}, 50-80 mL-min) were comparable to those of women with normal renal function (CL_{cr}, >80 mL/min). The serum drospirenone levels were on average 37% higher in women with normal renal

function. Drospirenone treatment was well tolerated by all groups. Drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

- *Effect of hepatic impairment*

In women with moderate hepatic function, (Child-Pugh B) mean serum drospirenone concentration-time profiles were comparable to those of women with normal hepatic function during the absorption/distribution phases with similar C_{max} values. The decline in serum drospirenone concentrations during the terminal disposition phase was about 1.8 times greater for volunteers with moderate hepatic impairment than for the volunteers with normal hepatic function.

An about 50% decrease in apparent oral clearance (CL/f) was seen in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate into any apparent difference in terms of serum concentrations between the two groups of volunteers. Even in the presence of diabetes and concomitant treatment with spironolactone (two factors that can predispose a patient to hyperkalemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that drospirenone is well tolerated in patients with mild or moderate hepatic impairment (Child-Pugh B).

- *Ethnic groups*

The impact of ethnic factors on the pharmacokinetics of drospirenone and ethinylestradiol was studied after single and repeated daily oral administration to young healthy Caucasian and Japanese women. The results showed that ethnic differences between Japanese and Caucasian women had no clinically relevant influence on the pharmacokinetics of drospirenone and ethinylestradiol.

Ethinylestradiol

Absorption

Orally administered Ethinylestradiol is rapidly and completely absorbed. , Peak serum concentrations of about 54-100 pg/ml are reached within 1-2 hours. During absorption and first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 20-65%. Concomitant intake of food reduced the bioavailability in about 25% of the investigated subjects while no change was observed in the others.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approx. 98 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2.8-8.6 l/kg was determined.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The clearance rate was reported to be about 2.3-7 ml/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases characterized by half-lives of about 1 hour and 10-20 hours, respectively. Unchanged drug is not excreted, ethinylestradiol metabolites. are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Steady-state conditions are reached during the second half of a treatment cycle when serum drug levels are higher by 40-110% as compared to single dose.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Modified maize starch
Povidone 25000
Magnesium stearate
Hydroxypropylmethyl cellulose
Macrogol 6000
Talc
Titanium dioxide
Ferric oxide pigment, yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

In a dry place

6.5 Nature and content of container

*** Primary packaging**

PVC blister (250 µm), at the back fitted with aluminum push through foil (20 µm).

*** Secondary packaging**

Each blister pack is packed in an aluminum-polyethylene pouch.

*** Presentation**

Calendar-pack containing 21 tablets

Calendar-pack containing 3x21 tablets

Manufacturer: Bayer Schering Pharma AG, Berlin, Germany

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