



Yasmin®

Film-coated tablet

1. NAME OF THE MEDICINAL PRODUCT

Yasmin 0.03 mg / 3 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 hormone-containing light yellow film-coated tablets:

Each film-coated tablet contains 0.030 mg ethinylestradiol, 3 mg drospirenone

For a full list of excipient(s) see section "List of excipients"

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1 Indication

For 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.

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 film-coated 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 a combined hormonal contraceptive (combined oral contraceptive /COC), vaginal ring, or transdermal patch*

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

► *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 of tablet-taking. 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 may be 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 this is not the case, or if she 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 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, the woman should be advised to follow the first of these two options and to 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 pack must be started as soon as the current 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

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 Contraindications

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).
- ▶ A high risk of venous or arterial thrombosis (see 'Special warnings and precautions for use').
- ▶ History of migraine with focal neurological symptoms.
- ▶ Diabetes mellitus with vascular involvement.
- ▶ Severe hepatic disease as long as liver function values have not returned to normal.
- ▶ Yasmin is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interaction with other medicinal products and other forms of interaction).
- ▶ 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 precautions for use

Warnings

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

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 life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A COC should not be prescribed in case of a negative risk benefit assessment. (see 'Contraindications')

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

- ▶ age;
- ▶ obesity (body mass index over 30 kg/m²);
- ▶ 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 in 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).

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir / ritonavir and dasabuvir therapy (See Section Contraindications and Section Interaction with other medicinal products and other forms of interaction).

Other conditions

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. 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; gallstone 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 < 0.05 mg 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.

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 increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:

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

Substances with variable effects on the clearance of COCs, e.g.:

When co-administered with COCs, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of COCs (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

Effects of COCs on other medicinal products

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

Based on in vivo interaction studies in female volunteers using omeprazole, simvastatin or midazolam as marker substrates, a clinically relevant interaction of drospirenone at doses of 3 mg with the cytochrome P450 mediated metabolism of other drugs is unlikely.

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

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Yasmin can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Serious adverse reactions are arterial and venous thromboembolism.

Tabulated list of adverse reactions

The frequencies of ADRs reported in clinical trials with Yasmin (N=4897) are summarised in the table below. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. Frequencies are defined as common ($\geq 1/100$ to $< 1/10$) and rare ($\geq 1/10,000$ to $< 1/1000$). Additional ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under 'not known'.

System Organ Class (MedDRA)	Common	Rare	Not known
Psychiatric disorders	Emotional lability Depression/ depressive mood Decrease and loss of libido		
Nervous system disorders	Migraine		
Vascular disorders		Venous and arterial thromboembolic events*	
Gastrointestinal disorders	Nausea		
Skin and subcutaneous tissue disorders			Erythema multiforme
Reproductive system and breast disorders	Breast pain Unscheduled uterine bleeding Genital tract bleeding not further specified		

Adverse events in clinical studies were coded using the MedDRA dictionary. Different MedDRA terms representing the same medical phenomenon have been grouped together as single adverse reactions to avoid diluting or obscuring the true effect.

- * - Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. Frequency was borderline to Very Rare.
 - 'Venous and arterial thromboembolic events' summarizes the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as hemorrhagic

For venous and arterial thromboembolic events and migraine see also sections 'Contraindications', 'Special warnings and precautions for use'.

The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 12.1.

Description of selected adverse reactions

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections "Contraindications", "Special warnings and precautions for use"):

Tumors

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

Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 'Interaction with other medicinal products and other forms of interaction').

4.8 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 withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicinal product. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic properties

Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Peak serum concentrations of approximately 37 ng/ml are reached at about 1 - 2 h after single 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 extensively metabolized after oral administration. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfatation. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4. The clearance rate from serum is about 1.2-1.5 ml/min/kg.

Elimination

Drospirenone serum 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 to urinary 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

► *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 of ethinylestradiol 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 (approximately 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 significant gut and hepatic first-pass metabolism. Ethinylestradiol and its oxidative metabolites are primarily conjugated with glucuronides or sulfate. The metabolic 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

List of excipients