# 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

Excipient: lactose 46 mg

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

# 3. PHARMACEUTICAL FORM

Film-coated tablet

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

# 4. CLINICAL PARTICULARS

## 4.1 Indication(s)

Oral contraceptive, with antimineralocorticoid and antiandrogenic effects also beneficial for women who experience hormone-related fluid retention and the resulting symptoms and for women with acne and seborrhea.

## 4.2 Dosage and method of administration

### 4.2.1 Method of administration

Oral use

### 4.2.2 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.

*How to start Yasmin*

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding).

*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.

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.

### 4.2.3 Additional information on special populations

#### 4.2.3.1 Pediatric patients

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

#### 4.2.3.2 Geriatric patients

Not applicable. Yasmin is not indicated after menopause.

#### 4.2.3.3 Patients with hepatic impairment

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

#### 4.2.3.4 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.
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these (see '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 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.

VTE may be life-threatening or may have a fatal outcome (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.

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 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/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 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).

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 liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

Malignancies may be life-threatening or may have a fatal outcome.

*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.

***Medical examination/consultation***

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.

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 medicinal products on Yasmin***

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

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

Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the 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***

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in ALT levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see 'Contraindications').

***Other forms of interaction***

*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.

- *Laboratory tests*

The use of contraceptive steroids may influence the results of certain laboratory tests.

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

## 4.6 Pregnancy and lactation

### 4.6.1 Pregnancy

Yasmin is not indicated during pregnancy. If pregnancy occurs during treatment with Yasmin, further intake must 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.

### 4.6.2 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 or use machines

## 4.8 Undesirable effects

### 4.8.1 Summary of the safety profile

The most commonly reported adverse reactions with Yasmin are nausea and breast pain. They occur in > 6 % of users.

Serious adverse reactions are arterial and venous thromboembolism.

### 4.8.2 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 (≥ 1/100 to < 1/10) and rare (≥ 1/10,000 to < 1/1,000). 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<br>Depression/ depressive mood<br>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<br>Unscheduled uterine bleeding<br>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.*

### 4.8.3 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 COC use is unknown.
- Liver tumors (benign and malignant)

*Other conditions*

- Erythema nodosum
- Women with hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: 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
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis.
- Chloasma
- Hypersensitivity (including symptoms such as rash, urticaria)

*Interactions*

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').

### 4.9 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 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

Pharmacotherapeutic group: 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.

Post Authorization Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges between 7-10 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 per 10,000 woman years in non-pregnant non-COC users, and ranges between 20 to 30 per 10,000 pregnant women or postpartum.

The increased risk of VTE associated with COC use is attributed to the estrogen component. There remains a scientific debate regarding any modulating effect on the risk of VTE by the progestin component of COCs. Epidemiological studies that compared the risk of VTE associated with use of ethinylestradiol/drospirenone to the risk with use of COCs containing levonorgestrel reported differing results ranging from no difference in risk to a three-fold increase in risk. The majority of studies investigated Yasmin.

Two post approval commitment studies have been completed specifically for ethinylestradiol/drospirenone 0.03 mg/3 mg (Yasmin). In one, prospective active surveillance study, the incidence of VTE in women with or without other risk factors for VTE who used Yasmin was found to be in the same range as that for users of levonorgestrel-containing COCs and other COCs (various other COC brands). The other, a prospective, controlled, database study comparing users of Yasmin to other COC users also confirmed a similar incidence of VTE among all of the cohorts.

As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (see 'Special warnings and precautions for use', '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 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 CYP 3A4

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*

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 serum drospirenone levels in women with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those of women with normal renal function (CLcr, >80 mL/min). The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CLcr, 30 - 50 mL/min) compared to those 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 Cmax values. The mean terminal half-life of drospirenone for volunteers with moderate hepatic impairment was 1.8 times greater than for 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 potassium 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 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. **Error! Bookmark not defined.** 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

ferric oxide pigment, yellow
hydroxylpropylmethyl cellulose
lactose monohydrate
macrogol 6000
magnesium stearate
maize starch (corn starch)
modified starch (pregelatinized starch)
povidone 25000
talc
titanium dioxide

### 6.2 Incompatibilities

None

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Do not store above 30°C
Keep out of reach of children
**Only on Prescription**

## 6.5 Nature and contents of container

Aclar Blister Pack: 1 x 21 Tablets

## 6.6 Instructions for use / handling

None

## 6.7 Manufactured by:

Bayer AG

Physical Address

Muellerstr. 178,

13353 Berlin

Postal Address

13342 Berlin

Germany

## 6.8 Date of revision of text: July 2017

Ref: xCCDS #17 (BEC 10462)