

YASMIN[®]

Drospirenone/Ethinylestradiol Tablets

Presentation

YASMIN: The memo-pack holds 21 round, light yellow, film-coated tablets containing 3 mg drospirenone and 30 µg ethinylestradiol. The tablets are embossed with the letters “DO” in a regular hexagon.

The memo-pack also contains 7 round white placebo tablets, embossed with the letters “DP” in a regular hexagon.

Uses

Actions

YASMIN is a combined oral contraceptive tablet containing the synthetic progestogen, drospirenone, and the synthetic oestrogen, ethinylestradiol. The contraceptive effect of YASMIN is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in cervical secretion. When YASMIN is taken according to instructions, the egg cells are prevented from maturing to the point at which they can be fertilised, the cervical mucus remains thick so as to constitute a barrier to sperm, and the endometrium is rendered unreceptive to implantation.

As well as protection against pregnancy, oestrogen/progestogen combinations have several positive properties which, next to the negative properties, 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. In addition, with the higher dosed combined oral contraceptives COCs (50 µg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breast, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs remains to be confirmed.

Drospirenone has antimineralocorticoid activity, counteracting oestrogen related sodium retention. In combination with ethinylestradiol, drospirenone displays a favourable lipid profile with an increase in high-density lipoprotein HDL. Drospirenone exerts antiandrogenic activity and does not counteract the ethinylestradiol-related sex hormone binding globulin (SHBG) increase which is useful for binding and inactivating the endogenous androgens.

Drospirenone is devoid of any androgenic, oestrogenic, 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.

Drospirenone

- Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum serum concentrations of about 37 ng/mL are reached at about 1 - 2 hours after single ingestion. Absolute bioavailability is between 76 and 85%. Concomitant ingestion of food has no influence on bioavailability.

- Distribution

After oral administration, serum drospirenone levels decrease in two phases which are characterised by half-lives of 1.6 ± 0.7 hours and 27.0 ± 7.5 hours, respectively. Drospirenone is bound to serum albumin and does not bind to 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 ethinyloestradiol induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is about 3.7 – 4.2 L/kg.

- Metabolism

Drospirenone is extensively metabolised after oral administration. 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-sulphate, both of which are formed without involvement of the P450 system. Drospirenone is metabolised to a minor extent by cytochrome P450 3A4 based on *in vitro* data. When drospirenone was acutely co-administered with ethinyloestradiol, no direct interaction was found.

- Elimination

The metabolic clearance rate from serum is about 1.2 – 1.5 mL/min/kg. Drospirenone is not excreted in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is about 40 hours.

- Steady-State Conditions

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 60 ng/mL are reached between day 7 and day 14 of treatment. Serum drospirenone levels accumulated by a factor of 2 to 3 as a consequence of the ratio of terminal half-life and dosing interval. Further accumulation of drospirenone levels beyond treatment cycles was observed between cycles 1 and 6 but thereafter, no further accumulation was observed.

Special Populations

Effect of renal impairment

Steady-state serum 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 moderate renal impairment (CL_{cr}, 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 C_{max} values. The decline in serum drospirenone concentrations during the terminal disposition phase was about 1.8 times greater for the 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 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 hyperkalaemia, an increase in serum potassium concentrations above the upper limit of the normal range was not observed. Based on the results of this study it can be concluded that drospirenone/ethinyloestradiol 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 ethinyloestradiol 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 ethinyloestradiol.

Ethinyloestradiol

- Absorption

Orally administered ethinyloestradiol is absorbed rapidly and completely. Peak serum concentrations of about 54 - 100 pg/mL are reached within 1 - 2 hours after single oral administration. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%. Concomitant intake of food had a variable effect. The maximum concentration was reduced in all subjects and the bioavailability of

ethinyloestradiol was reduced in about 25% of the investigated subjects while no change was observed in the others.

- Distribution

Serum ethinyloestradiol levels decrease in two phases, the terminal disposition phase is characterised by a half-life of approximately 24 hours. Ethinyloestradiol 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

Ethinyloestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. It is primarily metabolised 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 sulphate. The metabolic clearance rate of ethinyloestradiol is about 2.3 - 7 mL/min/kg.

- Elimination

Ethinyloestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinyloestradiol 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 and serum levels of ethinyloestradiol accumulate by a factor of 1.4 - 2.1.

Clinical Trials

2,274 women have received YASMIN in clinical studies over study periods between 6 and 26 cycles, giving a total of 30,110 cycles. The assessment of the contraceptive efficacy was based on seven phase II and phase III studies. These studies comprised 2,263 valid cases for the efficacy evaluation and 29,735 cycles. Five of these studies were comparative studies. The observation periods were between 6 and 26 cycles. For the calculation of the Pearl Index, all cycles in which at least 19 tablets were taken were counted, as were all pregnancies under treatment. This gives a slight over-estimation of the true Pearl Index. For the corrected Pearl Index calculation cycles in which condom use was documented were excluded.

The uncorrected Pearl Index was 0.57. The corrected Pearl Index, discounting pregnancies due to documented user failure was 0.09. In comparative studies the Pearl Index for desogestrel 150 mg and ethinyloestradiol 30 µg was 0.43 and 0.09 respectively. The results for both preparations were comparable to the range known for other low dosed oral contraceptives containing 30 µg ethinyloestradiol.

For YASMIN treated women the probability of becoming pregnant for the time of continuous use was estimated. After two years of YASMIN use, the estimated failure rate was still below 0.01.

Cycle control was evaluated on the basis of 2 extended phase III studies in 1,313 women taking YASMIN. The total number of cycles valid for analysis was 20,787. Between 40 - 60% of women reported intermenstrual bleeding, however the number of cycles with bleeding was only 7.5 - 9%. Between 75 - 80% of women had no irregular bleeding in the first cycle. This increased 85 - 90% in the next 2 cycles. A constant low frequency of less than 10% was observed through the end of both studies (13 and 26 cycles). Spotting occurred in 6 - 7% of all cycles and heavy/normal breakthrough bleedings in less than 0.5% of cycles. Spotting and breakthrough bleeding combined occurred in less than 2% of all cycles. The incidence of amenorrhoea was less than 1% and 1.6% in the two studies.

YASMIN produced a decrease in the duration and intensity of the withdrawal bleed. YASMIN had no adverse effect on blood pressure or body weight.

Indications

Oral contraception

Dosage and Administration

YASMIN is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection.

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. Tablet taking is continuous. One tablet is taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2 - 3 after starting the placebo tablets and may not have finished before the start of the next pack.

How to Start YASMIN

START WITH THE FIRST TABLET FROM THE GREEN SECTION MARKED WITH THAT DAY OF THE WEEK, in accordance with one of the following:

- 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). The women should be instructed to take a

yellow hormonal tablet from the green section of the pack, corresponding to that day of the week. If started on day 1 in this way, protection against pregnancy is immediate and no additional methods of contraception are required. Starting on days 2 - 5 is allowed, but if this occurs a barrier contraceptive method is recommended in addition for the first 7 days of tablet taking.

- Changing from another combined oral contraceptive (COC) vaginal ring, or transdermal patch

The woman should start with YASMIN preferably on the day after the last hormonal 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 vaginal ring or transdermal patch has been used, the woman should start using Yasmin preferably on the day of 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 or IUS on the day of its removal, or from an injectable when the next injection would be due), but should in all of these cases, the woman should be advised to additionally use a barrier contraceptive 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 *Use in Lactation*.

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

Management of Missed Tablets

Missed white pills from the last row of the blister are placebo tablets and thus can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only refers to missed active tablets (rows 1 – 3 of the blister):

If the user is **less than 12 hours** late in taking any hormonal 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 hormonal tablet, contraceptive protection may be reduced.

There is a particularly high risk of pregnancy if tablets are missed at the beginning or end of the pack. If tablets are missed in the first week of taking hormonal tablets and intercourse took place in the preceding 7 days, the possibility of pregnancy should be considered. 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. Seven 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 pregnancy should be considered. The more tablets are missed and the closer they are to the placebo tablet phase the higher the risk of 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 placebo tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there would be 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 until all the hormonal tablets are used up. The 7 tablets from the last row (placebo) must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the hormonal tablets 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 pack. She should then have a tablet-free interval for 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 following placebo tablet week, the possibility of 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 (see above) is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to Shift Periods or How to Delay a Period

To delay a period the woman should continue with hormonal tablets from another calendar pack of YASMIN without taking the placebo tablets from her current calendar pack. The extension can be carried on for as long as desired until the end of the second calendar pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of YASMIN is then resumed with the next pack.

Contraindications

Preparations containing oestrogen/progestogen combinations 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 their use, the product should be stopped immediately.

- Thrombosis (venous or arterial) present or in history (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident)
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris)

- Presence or history of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- Disturbed lipometabolism
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see WARNINGS and PRECAUTIONS)
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Severe renal insufficiency or acute renal failure
- Presence or history of liver tumours (benign or malignant)
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the components of YASMIN

Warnings and Precautions

The clinical and epidemiological evidence for oestrogen/progestogen combinations like YASMIN is predominantly based on experience with COCs in general. Therefore, the following warnings related to the use of COCs apply also to the use of YASMIN.

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 COC use should be discontinued.

- **Circulatory Disorders**

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

Venous thromboembolism (VTE) manifesting as deep venous thrombosis and/or pulmonary embolism may occur during the use of all COCs. The risk of VTE is highest during the first year a woman takes a COC. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) with the same or a different COC. Data from a large, prospective 3-armed cohort study (EURAS, 2007 and LASS, 2009) suggests that this increased risk is mainly present during the first 3 months.

Epidemiological studies have suggested that the incidence of VTE in women with no known risk factors for VTE who take low dose oestrogen (< 50 µg ethinyloestadiol) COCs ranges from about 20 cases per 100,000 woman-years (for COCs containing levonorgestrel) to 40 cases per 100,000 woman-years (for COCs containing desogestrel or gestodene). This compared with 5 – 10 cases per 100,000 woman-years for non-users and 60 cases per 100,000 pregnancies. VTE may be life-threatening or may have a fatal outcome (in 1 – 2% of the cases).

A recently conducted, large (approximately 140,000 women years (WY) of observation), prospective, multinational, cohort study on the safety of OC use, (the EURAS study) showed the risk of VTE in users of COCs containing drospirenone to be comparable to that of those containing levonorgestrel (second-generation). A further prospective cohort study (Ingenix) showed a comparable risk of thrombosis in users of COCs containing drospirenone and other COC users, including levonorgestrel. For details see the following table from the EURAS study:

Incidences* (with 95% Confidence Interval) of thromboembolic events in the EURAS Study#

Type of Event	YASMIN (28,621 WY)		LNG-containing (31,415 WY)		Other OC's (52,623 WY)	
	Incidence+	95% CI	Incidence+	95% CI	Incidence+	95% CI
VTE* & ATE** combined	9.8	6.5 – 14.1	10.8	7.5 – 15.1	11.6	8.9 – 14.9
VTE* only	9.1	5.9 – 13.3	8.0	5.2 – 11.7	9.9	7.4 – 13.0
ATE** only	0.7	0.1 – 2.5	2.9	1.3 – 5.4	1.7	0.8 – 3.2
All cause Mortality	1.4	0.4 – 3.6	2.5	1.1 – 5.0	1.7	0.8 – 3.2

* Incidence is given in events per 10,000 Women Years (WY)

* Venous-thromboembolic Events (VTE) comprises Deep Vein Thromboses and Pulmonary Embolism

** Arterial-thromboembolic Events (ATE) comprises Cerebral Vascular Accident and Acute Myocardial Infarction

#Final study results: April 2006

Two additional epidemiological studies, one case control study (van Hylckama Vlieg et al, 2009) and one retrospective cohort study (Lidegaard et al, 2009) suggested that the risk of venous thromboembolism occurring in YASMIN users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so called third generation COCs). In the case-control study, however, the number of YASMIN cases was very small (1.2% of all cases making the risk estimates

unreliable). The relative risk for YASMIN users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the products for 1 to 4 years, the relative risk was similar for users of YASMIN to that of other COC products.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal 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 COCs.

Symptoms of venous (includes pulmonary embolism (PE) and deep venous thrombosis (DVT)) or arterial thrombotic/thromboembolic (includes myocardial infarction (MI), vascular occlusion and cerebrovascular accident) events can include: unilateral leg pain and/or swelling; 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; sudden severe pain in the chest which may increase with deep breathing; 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe, prolonged headache with no known cause; sudden, partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; "acute" abdomen, fullness, indigestion or choking feeling; sweating; nausea; vomiting.

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).

Arterial thromboembolic events may be life threatening or may have a fatal outcome.

The risk of thromboembolism (venous and/or arterial) or of a cerebrovascular accident increases with:

- age
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- 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 suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

- obesity (body mass index over 30 kg/m²)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- prolonged immobilisation, 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 remobilisation.

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.

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

An increase in frequency or severity of headaches during COC use in particular the onset of migraine (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 ethinylloestradiol).

• **Tumours**

The most important risk factor for cervical cancer is persistent human papilloma virus (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 an 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, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

- **Other Conditions**

Potassium excretion 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 hyperkalaemia can be assumed only for patients whose pretreatment serum potassium is in the upper reference range, and who are additionally using potassium-sparing medicines.

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 ethinylloestradiol-induced increases in blood pressure observed in normotensive women using other COCs. A relationship between COC use and clinical hypertension has not been established. 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; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

Acute or chronic disturbances of liver or kidney function may necessitate the discontinuation of COC use until markers of liver or kidney 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 (containing 50 µg ethinyloestradiol) COCs. 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 light yellow active tablet contains 48.17 mg of lactose and each white placebo tablet contains 52.14 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

- Check the following before use:

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of YASMIN, guided by the “*Contraindications*” and “*Warnings and Precautions*” sections. This should be repeated at least annually during the use of YASMIN. Periodic 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 YASMIN. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Diseases including HIV infections and AIDS

Women should be advised that preparations like YASMIN do not protect against HIV infections (AIDS) and other sexually transmissible diseases. Women should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs.

Reduced Efficacy

The efficacy of YASMIN may be reduced in the event of missed tablets, gastrointestinal disturbances (e.g. vomiting, diarrhoea) during hormonal tablet-taking or concomitant medication.

Reduced Cycle Control

With oestrogen/progestogen combinations, 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 while taking the 7 placebo tablets. If the COC has been taken according to the directions, 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.

Use in Pregnancy

The administration of YASMIN is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. If pregnancy occurs during treatment with YASMIN the preparation must be discontinued immediately.

Drospirenone and/or its metabolites crossed the placenta and entered the foetus when administered orally to pregnant rats and rabbits. Treatment of pregnant rats with a combination of drospirenone and ethinyloestradiol resulted in a dose-dependent increased incidence of embryoletality due to increased pre- and post-implantation losses. There was no indication of teratogenic effects of drospirenone in rabbits or rats.

Dose-dependent feminisation of male foetuses and virilisation of female foetuses were seen following administration of a combination of predrospirenone and ethinyloestradiol to female rats in the last third of pregnancy. Feminising effects in male foetuses were consistent with drospirenone's anti-androgenic activity and were observed at an estimated systemic exposure approximately 8 - 13 folds than that anticipated clinically (based on AUC). Virilisation of female foetuses was seen following systemic drospirenone exposure of approximately 2 - 5 fold than that anticipated clinically (based on AUC). This effect has previously been described for oestrogens in rats. When pregnant monkeys received a combination of drospirenone and ethinyloestradiol by daily oral administration during the major period of organogenesis and sexual organ differentiation, abortion rates were increased in a dose-dependent manner. However there were no indications of teratogenicity.

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. See also “*Contraindications*”.

The available data regarding the use of YASMIN during pregnancy is too limited to permit conclusions concerning negative effects of YASMIN on pregnancy, health of the foetus or neonate.

Use in 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 in the milk.

Paediatric Use

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

Use in the Elderly

Yasmin is not indicated after menopause.

Patients with hepatic impairment

Yasmin is contraindicated in women with severe hepatic diseases. See CONTRAINDICATIONS.

Patients with renal impairment

Yasmin is contraindicated in women with severe renal insufficiency or acute renal failure. See CONTRAINDICATIONS.

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 the ability to drive and use machines have been observed in users of COCs.

Preclinical Safety Data

Animal toxicity studies for human risk estimation were performed for both components of the preparation, ethinylloestradiol and drospirenone, and in certain cases with the combination.

No effects which might indicate an unexpected risk to humans were observed during systemic tolerance studies after repeated administration.

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 might stimulate the growth of hormone-dependent tissues and tumours.

Studies on embryotoxicity and teratogenicity and the evaluation of effects of the combination on the fertility of parent animals, foetal development, lactation and reproductive performance of the offspring gave no indication of a risk of adverse effects in humans after recommended use of the preparation. Especially, the feminising effect in male rat foetuses after treatment of pregnant animals during the sensitive phase of foetal sex differentiation does not raise concerns with regard to human safety assessment since it occurred only after drug exposures which are substantially higher than those observed in users of YASMIN.

Although interactions between drospirenone and DNA of liver cells which indicate a genotoxic potential were found in *in vitro* and *in vivo* studies on rats, no such finding was observed in human liver cells *in vitro*. Furthermore, mutagenicity tests gave no indication of a mutagenic potential of the compound. Thus current knowledge indicates no relevant mutagenic potential.

Adverse Effects

Serious undesirable effects of YASMIN have been referred to in the “*Contraindications*” and “*Warnings and Precautions*” sections. These include venous and arterial thromboembolic disorders.

The following undesirable effects have been reported in users of COCs and whether this association is causal has not been confirmed:

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Immune system disorders			Hypersensitivity
Investigations	Weight increased		Weight decreased
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood,	Libido decreased	Libido increased

	mood altered		
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

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

Interactions

Interactions between oral contraceptives and other medicines may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism: Interactions can occur with medicines 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 (*Hypericum perforatum*)).

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

Interference with Enterohepatic Circulation: Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic agents are given, which may reduce ethinyloestradiol concentrations (e.g. penicillins, tetracyclines).

Women on treatment with any of these medicines should temporarily use a barrier method in addition to the COC or choose another method of contraception. With microsomal enzyme-inducing medicines, 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 active tablets in the COC pack, the placebo tablets should be omitted and the next COC pack be started.

Women on long-term treatment with hepatic-enzyme inducing drugs, experts have recommended to increase the contraceptive steroid doses. If a high contraceptive dosage is most desirable or appears to be unsatisfactory or unreliable, e.g. in the case of irregular bleeding, another method of contraception should be advised.

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.

Oral contraceptives may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

- Influence of YASMIN on other medicines

Based on *in vitro* inhibition studies and an *in vivo* interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrates, drospirenone at doses of 3 mg shows little propensity to interact with the metabolism of other medicines.

- Other interactions

There is theoretical potential for an increase in serum potassium in women taking YASMIN with other medicines that may increase serum potassium levels. Such medicines include: angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in a study evaluating the interaction of drospirenone (combined with oestradiol) with an ACE inhibitor no clinically or statistically significant differences in serum potassium concentrations in mildly hypertensive postmenopausal women maintained on enalapril therapy were observed in comparison with placebo.

Prescribing information of concomitant medications should be consulted to identify potential interactions.

- **Laboratory Tests**

The use of preparations like YASMIN 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.

Overdosage

There has not yet been any clinical experience of overdose with YASMIN. There have been no reports of serious deleterious effects from overdose in preclinical studies. On the basis of general experience with COCs, symptoms that may occur in case of taking an overdose are: nausea, vomiting and in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

In cases of overdose, it is advisable to contact the National Poisons Information Centre (0800 764 766) for recommendations on the management and treatment of overdose.

Pharmaceutical Precautions

Shelf life: 3 years

Storage conditions: Store below 25 °C

Medicine Classification

Prescription Medicine

Package Quantities

3 calendar-packs each containing 28 tablets

Further Information

List of Excipients

Lactose monohydrate, maize starch (corn starch), pre-gelatinised starch, povidone, magnesium stearate, hypromellose, macrogol 6000, purified talc, titanium dioxide, iron oxide yellow.

Instructions for Use/Handling

Store all drugs properly and keep them out of reach of children.

Name and Address

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Date of Preparation

10 March 2011