

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Yasmin® 30 micrograms / 3 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active light yellow tablet contains:

Ethinylestradiol	30 micrograms
Drospirenone	3 mg

For full list of excipients, see section 6.1 *List of excipients*.

3. PHARMACEUTICAL FORM

YASMIN active tablet

Light yellow round film-coated tablets marked on one side with the letters "DO" in a regular hexagon, each containing drospirenone 3 mg and ethinylestradiol 30 µg.

YASMIN placebo tablet

White, round placebo film-coated tablets, marked on one side with the letters "DP" in a regular hexagon.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

4.2 Dose and method of 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 white placebo tablets and may not have finished before the next pack is started.

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 light yellow active 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 of the menstrual cycle is allowed, but during the first 7 days of the first cycle, a barrier contraceptive method is recommended in addition to tablet taking.

- **Changing from another 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 active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.

In case vaginal ring or transdermal patch has been used, the woman should start using Yasmin preferably on the day of removal of the ring or patch, 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 from the minipill on any day, from an implant or IUS on the day of its removal, or from an injectable when the next injection would be due. However, in all of these cases, the woman must 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**

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.

For breastfeeding women see *4.6 Fertility, pregnancy and lactation*.

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 light yellow active tablets (rows 1 – 3 of the blister):

If the woman is **less than 12 hours** late in taking any light yellow active 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 light yellow active 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 active 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. Active (hormonal) tablet-taking must never be discontinued for longer than 7 days
2. Seven days of uninterrupted active (hormonal) 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 woman 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 woman 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 woman 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 active 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 active 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 light yellow active tablets from another calendar pack of YASMIN without taking the white 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.

4.3 Contraindications

Preparations containing estrogen/progestogen combinations including YASMIN 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.

- Presence or risk of venous thromboembolism (VTE) (see *4.4 Special warnings and precautions for use*)
 - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE]
 - Known hereditary or acquired predisposition for VTE, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
 - Major surgery with prolonged immobilisation
 - A high risk of VTE due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see *4.4 Special warnings and precautions for use*)
 - Current ATE or history of ATE (e.g. myocardial infarction [MI] or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
 - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant)

- History of migraine with focal neurological symptoms
- A high risk of ATE due to multiple risk factors or to the presence of one serious risk factor such as:
 - diabetes mellitus with vascular symptoms
 - severe hypertension
 - severe dyslipoproteinaemia
- 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
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these (see 4.5 *Interaction with other medicines and other forms of interaction*)
- 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

4.4 Special warnings and precautions for use

The clinical and epidemiological evidence for estrogen/progestogen combinations like YASMIN is predominantly based on experience with combined oral contraceptives (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 containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any COC increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective, multinational cohort study (EURAS, 2007 and LASS, 2009) on the safety of COC use suggests that this increased risk is mainly present during the first 3 months.

A number of studies have compared the risk of VTE for users of ethinylestradiol/drospirenone 30 µg/3 mg to the risk for users of other COCs, including COCs containing levonorgestrel.

Epidemiological studies have suggested that the incidence of VTE in women with no known risk factors for VTE who take low dose estrogen (< 50 µg ethinylestradiol) 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. A 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.

In 2011 a re-analysis of the retrospective cohort study estimated the VTE risk of users of drospirenone 30 µg to be approximately twice that of users of levonorgestrel. However, the re-analysis was also affected by some of the same flaws as the original analysis such as lacking

validation of VTE diagnosis. It also contained substantial inconsistencies compared to the original study with regard to the duration of use effect.

Another retrospective cohort study by Sidney S., reported a higher risk of VTE when comparing drospirenone 30 µg to levonorgestrel COCs, however, the study had some methodological deficiencies, such as incomplete outcome validation, sociodemographic differences between the study populations, inability to account for some important confounding factors.

It is important that women understand that VTE associated with COC use is rare in average-risk women. The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the postpartum period (45-65 per 10,000 women over 12 weeks) is higher than that as associated with COC use.

Drospirenone containing COCs may be associated with a higher risk of VTE than COCs containing the progestogen levonorgestrel or some other progestogens. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase.

An additional increase in VTE risk for COCs containing ≥ 50 µg ethinylloestradiol cannot be excluded.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with COCs, and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting YAZ. See *4.2 Dose and method of administration* and *4.6 Fertility, pregnancy and lactation*.

VTE may be life-threatening or may have a fatal outcome (in 1-2% of the cases).

Extremely rarely, thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

The risk for venous thromboembolic complications in COC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

YASMIN is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors

- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
- Other medical conditions associated with VTE include
 - Cancer
 - Systemic lupus erythematosus
 - Haemolytic uraemic syndrome
 - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
 - Sickle cell disease
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of YASMIN (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if YASMIN has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

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

Symptoms of VTE (DVT and PE)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot 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 discoloured 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 be associated with haemoptysis
- sharp chest pain or sudden severe pain in the chest which may increase with deep breathing
- 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).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of COCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA).

Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in COC users increases in women with risk factors. YASMIN is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed.

Risk factors for ATE

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant).
- Migraine
- Other medical conditions associated with adverse vascular events:
 - Diabetes mellitus
 - Hyperhomocysteinaemia
 - Valvular heart disease
 - Atrial fibrillation
 - Dyslipoproteinaemia
 - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a COC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

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.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of a stroke can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body

- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, slurred speech or aphasia
- sudden partial or complete loss of vision; diplopia
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizure

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction 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
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats

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.

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

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 ethinylestradiol-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 estrogens 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 ethinylestradiol) 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 monohydrate and each white placebo tablet contains 23.21 mg of lactose monohydrate. 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.

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 "*Special warnings and precautions for use*" 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 Infections (STIs) including Human Immunodeficiency Virus (HIV) infections and Acquired Immuno Deficiency Syndrome (AIDS)

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

Reduced Efficacy

The efficacy of YASMIN may be reduced in the event of missed light yellow active tablets, gastrointestinal disturbances (e.g. vomiting, diarrhoea) during active tablet-taking or concomitant medication (see *4.2 Dose and method of administration* and *4.5 Interaction with other medicines and other forms of interaction*).

Reduced Cycle Control

With estrogen/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.

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 *4.3 Contraindications*.

Patients with Renal Impairment

Yasmin is contraindicated in women with severe renal insufficiency or acute renal failure. See *4.3 Contraindications*.

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.

4.5 Interaction with other medicines and other forms of interaction

Effects of other Medicines on Yasmin

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or oral 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 prescribed any of these medicines 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 medicine administration and for 28 days after their discontinuation. If the period in which the barrier method is used runs beyond the end of the active tablets in the COC pack, the white placebo tablets should be omitted and the next COC pack be started.

- **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 (*Hypericum perforatum*).

- **Substances with variable effects on the clearance of COCs**

When co-administered with COCs, many HIV/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestogen. 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. ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestogen or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol by 1.4 to 1.6-fold respectively, when taken concomitantly with a COC containing 35 µg ethinylestradiol.

Effects of COCs on Other Medicines

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

Based on *in vitro* inhibition studies and an *in vivo* interaction studies in female volunteers using omeprazole, simvastatin or midazolam as marker substrates, drospirenone at doses of 3 mg shows little propensity to interact with the cytochrome P450 mediated metabolism of other medicines.

In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol led to no, or a weak increase in CYP3A4 substrates (e.g. midazolam) and a weak (e.g. theophylline) to moderate (e.g. melatonin, tizanidine) increase in CYP1A2 substrates.

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 alanine aminotransferase (ALT) levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see '4.3 Contraindications').

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 estradiol) 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.

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

4.6 Fertility, pregnancy and lactation

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 ethinylestradiol resulted in a dose-dependent increased incidence of embryolethality 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 ethinylestradiol 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 estrogens in rats. When pregnant monkeys received a combination of drospirenone and ethinylestradiol 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 "4.3 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.

Breastfeeding

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.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable effects

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.

The most commonly reported adverse reactions 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 $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$) and rare ($\geq 1/10000$ to $< 1/1000$) Serious adverse reactions are arterial and venous thromboembolism. Additional ADRs identified only during post marketing surveillance, and for which a frequency could not be estimated are listed under 'not known'.

Tabulated List of Adverse Reactions

System Organ Class	Common	Uncommon	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 (version 12.1). 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' summarises 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 haemorrhagic

For venous and arterial thromboembolic events and migraine see also *4.3 Contraindications* AND *4.4 Special warning and precautions for use*.

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 COCs are listed below (see also '*4.3 Contraindications*' and '*4.4 Special warning and precautions for use*' sections):

Tumours

- 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 tumours (benign and malignant)

Other conditions

- Erythema nodosum
- Women with hypertriglyceridaemia (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; haemolytic 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)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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 withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche if they have accidentally taken YASMIN. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic effects

YASMIN is a combined oral contraceptive (COC) tablet containing the synthetic progestogen, drospirenone, and the synthetic estrogen, 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, COCs 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 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 antiminerlocorticoid activity, counteracting estrogen 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, estrogenic, glucocorticoid and antiglucocorticoid activity. This in combination with the antiminerlocorticoid and antiandrogenic properties, gives drospirenone a biochemical and pharmacological profile closely resembling the natural hormone progesterone.

Clinical efficacy and safety

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 ethinylestradiol 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 ethinylestradiol.

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.

5.2 Pharmacokinetic properties

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 ethinylestradiol 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.

Biotransformation

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, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalysed by cytochrome P450 3A4 and has demonstrated a capacity to inhibit this enzyme and cytochrome P450 1A1, cytochrome P450 2C9 and cytochrome P450 2C19 *in vitro*. When drospirenone was acutely co-administered with ethinylestradiol, 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 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 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/ethinylestradiol 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 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 ethinylestradiol was reduced in about 25% of the investigated subjects while no change was observed in the others.

Distribution

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

Biotransformation

Ethinylestradiol 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 ethinylestradiol is about 2.3 - 7 mL/min/kg.

Elimination

Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol 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 ethinylestradiol accumulate by a factor of 1.4 - 2.1.

5.3 Preclinical safety data

Animal toxicity studies for human risk estimation were performed for both components of the preparation, ethinylestradiol 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 fetuses 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
maize starch (corn starch)
pre-gelatinised starch
povidone
microcrystalline cellulose
magnesium stearate
hypromellose
macrogol 6000
purified talc
titanium dioxide
iron oxide yellow

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25 °C

6.5 Nature and contents of container

3 calendar-packs each containing 28 tablets

Yasmin tablets are contained in blister packs. Each blister contains 21 light yellow active tablets followed by 7 white placebo tablets.

6.6 Special precautions for disposal

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE CLASSIFICATION

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
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North Shore
AUCKLAND 0627

Free Phone: 0800 233 988

9. DATE OF FIRST APPROVAL

23 December 2004

10. DATE OF REVISION OF THE TEXT

22 March 2018

Summary table of changes

Section changed	Summary of new information
4.3 Contraindications	Updates regarding VTE and ATE.
4.4 Special warnings and precautions for use	Updates regarding the risk of VTE and ATE, including explanation about the risk factors and symptoms of VTE and ATE.

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