

AUSTRALIAN PRODUCT INFORMATION

YASMIN® (drospirenone & ethinylestradiol) tablet

1 NAME OF THE MEDICINE

YASMIN (drospirenone and ethinylestradiol)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each light yellow active tablet contains ethinylestradiol 30 µg and drospirenone 3 mg.

Excipients with known effect:

Each light yellow active tablet contains 48.17 mg of lactose monohydrate.

Each white placebo tablet contains 23.21 mg of lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Each YASMIN active tablet is light yellow, round and marked on one side with the letters "DO" in a regular hexagon.

Each YASMIN placebo tablet is white, round and marked on one side with the letters "DP" in a regular hexagon.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

YASMIN is indicated for use as an oral contraceptive.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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 method is recommended in addition to tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive/ COC) or vaginal ring

The woman should start with YASMIN preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.

In case a vaginal ring has been used, the woman should start taking YASMIN preferably on the day of removal of the ring, but at the latest when the next application would have been due. YASMIN should be started by taking a light yellow active tablet from the green section of the pack.

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 method for the first 7 days of tablet-taking.

Following first-trimester abortion

The woman may start tablet-taking immediately. When doing so, she does not need additional contraceptive measures.

Following delivery or second-trimester abortion

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

For breastfeeding women see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in lactation.

Management of missed tablets

Missed 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 the woman is more than 12 hours late in taking any light yellow active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. Active tablet-taking must never be discontinued for longer than 7 days.
2. Seven days of uninterrupted active 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 light yellow active tablet as soon as she remembers, even if this means taking two light yellow active tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days.

If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more light yellow active tablets are missed and the closer they are to the white placebo tablet phase the higher the risk of a pregnancy.

Week 2

The woman should take the last missed light yellow active tablet as soon as she remembers, even if this means taking two light yellow 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 light yellow active tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than one light yellow active 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 light yellow active 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 light yellow active tablet as soon as she remembers, even if this means taking two light yellow active tablets at the same time. She then continues to take tablets at her usual time until all the light yellow active tablets are taken. The 7 white placebo tablets from the last row must be discarded. The next pack must be started right away. The woman 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 of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

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

Advice in case of gastro-intestinal disturbances

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

If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets is applicable (see above). If the woman does not want to change her normal tablet-taking schedule, she should take the extra tablet(s) needed from another pack.

How to delay a period

To delay a period the woman should continue with active tablets from another pack of YASMIN without taking the white placebo tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack.

During the extension period, the woman may experience breakthrough bleeding or spotting. This is best managed by taking the placebo tablets to induce a withdrawal bleed than continuing active tablets. If the woman wishes to resume the 28 day dosing cycle, this may be done following the placebo tablet phase.

4.3 CONTRAINDICATIONS

Combined hormonal contraceptives (CHCs) 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 CHC use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see Section 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 venous thromboembolism, 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 venous thromboembolism due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
 - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
 - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant)
 - History of migraine with focal neurological symptoms
 - A high risk of arterial thromboembolism 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the ingredients contained in YASMIN

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Circulatory Disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing ethinylestradiol 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 combined hormonal contraceptive (CHC) 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 CHC is re-started after a break in use of 4 weeks or more.

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

Two prospective cohort studies (EURAS and Ingenix), each evaluating the risk of venous and arterial thromboembolism and death, were initiated separately at the time of YASMIN approval in Europe and the United States. The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in YASMIN users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC).

In the EURAS study, the VTE incidence rate for all OC users ranged from 8.0 to 9.9 per 10,000 WY. The overall incidence rate for past OC users was 4.7 VTE/10,000 WY, which was further specified to 19.4 VTE/10,000 WY for pregnant past OC users and 2.3 VTE/10,000 WY for non-pregnant past OC users. The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in YASMIN users compared to users of other COCs, including those containing levonorgestrel. In this second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed YASMIN.

Another large population based study (Heit et al) found an incidence rate of 20 VTE/10,000 WY in pregnant or postpartal women and 4.6 in non-pregnant women of reproductive age. All of these rates tend to be higher than those reported in the past. Based on this data it can be assumed that the VTE risk for OC users is roughly twice as high as for non-pregnant non OC users. The absolute attributable risk (approximately 4 VTEs per 10,000 WY of use) was found to be slightly higher in these studies than reported in the past. Nevertheless the risk in OC users remains lower than the VTE risk associated with pregnancy and the first weeks following delivery.

Two additional epidemiological studies, one case control study (van Hylckama Vlieg et al.) 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.

Two further retrospective database studies (Parkin et al., Jick and Hernandez) published in 2011, suggested a greater risk for VTE in users of drospirenone-containing COCs compared to levonorgestrel-containing COCs. However, the number of drospirenone cases in the Parkin et al. study was very small.

It is important that women understand that VTE associated with CHC 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 post-partum period (45-65 per 10,000 women over 12 weeks) is higher than that as associated with CHC 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 CHCs containing ≥ 50 μg ethinylestradiol 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 CHCs, and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting YASMIN (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy and Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in 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 CHC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

The risk for venous thromboembolic complications in CHC 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 CHC 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 CHC use.

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

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

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 CHC.

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 CHCs 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 CHC 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 CHC 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 CHC. 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 CHC use.

An increase in frequency or severity of migraine during CHC 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 CHC.

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 (MI) can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest arm, or below the breastbone
- discomfort radiating to the back, jaw, throat, arm, stomach
- 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 Papillomavirus (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 (Schlesselmann, Delgado-Rodriguez and Sillero-Arenas, Cox,

Edelman and Van Os), e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking 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 (Collaborative Group on hormonal factors in breast cancer).

In rare cases, benign liver tumours, 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 taking 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 taking other combined oral contraceptives. However, if a sustained clinically significant hypertension develops during the use of a COC, it is prudent for the doctor 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 uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics taking low-dose COCs (containing < 50 µg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs.

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

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Each 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 COC use, guided by the contraindications and precautions, and should be repeated at least annually during the use of COCs. 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 a COC. 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 Immune Deficiency Syndrome (AIDS)

Women should be advised that oral contraceptives do not protect against HIV and other STIs. Women should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced Efficacy

The efficacy of COCs may be reduced in the event of missed light yellow active tablets, gastro-intestinal disturbances during active tablet taking or concomitant medication (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and

Section 4.5 INTERACTIONS WITH OTHER MEDICINS AND OTHER FORMS OF INTERACTIONS).

Reduced Cycle Control

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

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

In some women withdrawal bleeding may not occur during the placebo tablet phase. 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 hepatic impairment

YASMIN is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see Section 4.3 CONTRAINDICATIONS).

Use in renal impairment

YASMIN is contraindicated in women with severe renal insufficiency or acute renal failure (see Section 4.3 CONTRAINDICATIONS).

Use in the elderly

YASMIN is not indicated after menopause.

Paediatric use

YASMIN is only indicated after menarche.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 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 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 certain 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 study in female volunteers taking 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 Section 4.3 CONTRAINDICATIONS).

Other Interactions

There is a 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 studies evaluating the interaction of drospirenone (combined with oestradiol) with an ACE inhibitor or indomethacin, no clinically or statistically significant differences in serum potassium concentrations were observed.

Note: The Product Information of concomitant medications should be consulted to identify potential interactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Pregnancy Category B3¹

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 embryoletality due to increased pre- and post-

¹ Category B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

implantation losses. There was no indication of teratogenic effects of drospirenone in rats or rabbits.

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 fold than that anticipated clinically (based on AUC). Virilisation of female foetuses was seen following systemic drospirenone exposure of approximately 2 to 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. YASMIN is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of YASMIN, the preparation must be discontinued immediately (see also Section 4.3 CONTRAINDICATIONS).

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most serious adverse reactions associated with the use of oral contraceptives are indicated under Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE (see also Section 4.3 CONTRAINDICATIONS).

Clinical trial data

The table below displays the adverse events reported by all patients receiving drospirenone preparations (2,991 patients) in the clinical trials. Of these, 2,614 patients received YASMIN.

Adverse event	Number of women affected	Percent of women affected
Gastrointestinal		
Nausea	265	9
Diarrhoea	119	4
Vomiting	76	3
Gastroenteritis	57	2
Body as a whole		
Pharyngitis	109	4
Cystitis	78	3
Sinusitis	56	2
Weight gain	27	<1
Weight loss	4	<1
Hypertension	7	<1
Hypotension	14	<1
Neurological		
Headache	599	20
Depression	107	4
Dizziness	76	3
Nervousness	59	2
Skin		
Acne	104	3
Reproductive		
Menstrual disorders	516	17
Breast pain	365	12
Vaginal candidiasis	166	6
Leukorrhoea	107	4
Intermenstrual bleeding	104	3
Vaginitis	24	<1

In addition, the following adverse events have been reported:

Psychiatric disorders: depression/depressive mood, emotional lability, decrease and loss of libido.

Reproductive system and breast disorders: unscheduled uterine bleeding, genital tract bleeding not further specified.

Skin and subcutaneous tissue disorders: Erythema multiforme (the frequency cannot be estimated from the available data and is therefore unknown, erythema nodosum, hypersensitivity (including symptoms such as rash, urticaria).

Nervous system disorders: migraine

Vascular disorders: venous and arterial thromboembolic events (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).

Post marketing data

The following undesirable effects have been reported in users of COCs and the association has been neither confirmed nor refuted:

breast tenderness, secretion, enlargement; altered mood; contact lens intolerance; vomiting; other gastrointestinal complaints (abdominal pain, diarrhoea); changes in vaginal secretion; fluid retention; change in body weight.

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The contraceptive effect of combined oral contraceptives is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. As well as protection against pregnancy, combined oral contraceptives have several positive properties which, next to the negative properties (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

Drospirenone has antimineralocorticoid 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. Drospirenone 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 antimineralocorticoid and antiandrogenic properties, gives drospirenone a biochemical and pharmacological profile closely resembling the natural hormone progesterone. Apart from this, with the higher-dosed combined oral contraceptives (COCs) (50 µg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs such as YASMIN remains to be confirmed.

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 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 the comparative studies the Pearl Index for Marvelon (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 OCs containing 30 µg ethinylestradiol.

For YASMIN treated women the probability of becoming pregnant for the time of continuous use was estimated. After 2 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 to 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.

Antimineralocorticoid efficacy

The clinical parameters of body weight, heart rate and blood pressure, which can be influenced by the antialdosterone properties of drospirenone were investigated in the framework of the phase II-III efficacy and cycle control studies. Body weight was assessed in two studies over periods of 13 and 26 cycles. Weight data was obtained from 1985 women on YASMIN and 822 women on Marvelon (ethinylestradiol 30 µg and desogestrel 150 µg). There was a reduction in body weight in the majority of women taking YASMIN and an increase with the women taking Marvelon. Mean changes in weight gain, cycles 1-13 were YASMIN -0.489kg and Marvelon +0.019kg. This difference between the two groups was statistically significant in both studies. Blood pressure was measured in all clinical studies at regular intervals. YASMIN had no adverse effect on blood pressure.

5.2 PHARMACOKINETIC PROPERTIES

Bioavailability studies have been conducted with YASMIN.

Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the drug in serum of about 35 ng/mL are reached at approximately 1-2 h after single ingestion. Bioavailability is between 76 and 85%. The intake of food had no influence on the extent of absorption but the maximum concentration was reduced as compared to drug intake on an empty stomach.

Distribution

After oral administration, serum drospirenone levels decrease in two phases which are characterised by half-lives of 1.6 ± 0.7 h and 27.0 ± 7.5 h, 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. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is 3.7 ± 1.2 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-sulfate, 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*.

Excretion

The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 mL/min/kg.

Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of approximately 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is approximately 40 h.

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 about 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.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 88 to 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.

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 98.5%), and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of approximately 5 L/kg was determined.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol 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 5 mL/min/kg.

Excretion

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 approximately 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 approximately 1.4 to 2.1.

5. PRECLINICAL SAFETY DATA

Genotoxicity

There is limited evidence available in the literature suggesting that estrogens may be weakly genotoxic at high doses. Ethinylestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells *in vitro*) and gave equivocal results in assays for chromosomal damage *in vitro* (clastogenic effects were not consistently seen and occurred at high concentrations). *In vivo* studies did not confirm these results.

Drospirenone was found to induce chromosome aberrations in human peripheral lymphocytes. However, drospirenone was not mutagenic in bacterial and mammalian cell gene mutation assays *in vitro*, and was not clastogenic in mouse micronucleus assays *in vivo*. Interactions between drospirenone and the DNA of liver cells which indicate a genotoxic potential were found in *in vitro* and *in vivo* studies in rats. No such finding was observed in human livers cells *in vitro*.

Carcinogenicity

Long-term carcinogenicity studies were performed in mice and rats with drospirenone, ethinylestradiol and with a combination of both products. After 2 years oral treatment of mice and rats with drospirenone alone there were no increases in the incidence of neoplastic lesions. Exposure to drospirenone (based on AUC) was up to 3-fold (mice) and 8- fold (rats) than that anticipated in humans at the recommended clinical dose. In contrast, treatment with the combination of drospirenone and ethinylestradiol resulted in an increased rate of neoplastic lesions in the mammary glands and uteri of mice and rats and in the pituitary glands of mice. The tumour pattern was similar but the incidence increased even further in animals receiving ethinylestradiol alone, indicating that ethinylestradiol was responsible for the increase in neoplastic lesions. Co-administration of

drospirenone decreased the carcinogenic potential of ethinylestradiol in the mouse pituitary and in the mouse and rat uterus and mammary gland.

The ethinylestradiol-induced tumours in rodents have previously been seen with other ethinylestradiol-containing products, and are considered attributable to species-specific effects of estrogens on prolactin secretion in rodents.

Although, long-term animal studies did not definitively indicate a tumourigenic potential for the clinical use of either drospirenone or ethinylestradiol, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each active tablet contains: lactose monohydrate, maize starch, pregelatinised maize starch, povidone, magnesium stearate, hypromellose, macrogol 6000, purified talc, titanium dioxide and iron oxide yellow.

Each placebo tablet contains: lactose monohydrate, microcrystalline cellulose, magnesium stearate, hypromellose, purified talc and titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

YASMIN tablets are contained in PVC/Aluminium blister packs. Each blister contains 21 round light yellow tablets followed by 7 round white placebo tablets.

Cartons contain memo packs of 1 x 28, 2 x 28, 3 x 28 or 4 x 28 tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

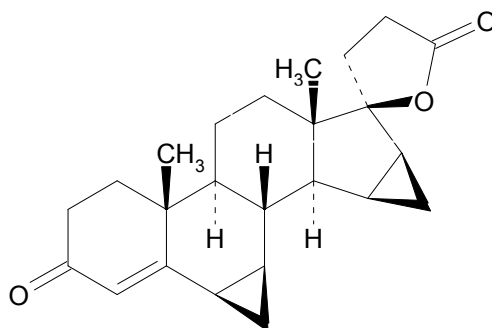
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Drospirenone

Chemical structure

The chemical name for drospirenone is 6 β , 7 β , 15 β , 16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21, 17-carbolactone and has the following structural formula:



Chemical formula: $C_{24}H_{30}O_3$

Molecular weight: 366.50

CAS number

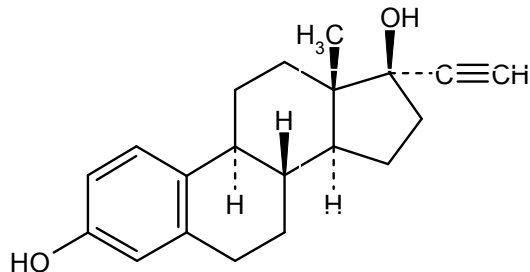
67392-87-4

Drospirenone is a white to off-white crystalline powder. It is freely soluble in methylene chloride, soluble in acetone, methanol, sparingly soluble in ethylacetate and ethanol 96% (v/v) and practically insoluble in hexane and water.

Ethinylestradiol

Chemical structure

The chemical name for ethinylestradiol is 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3, 17 β -diol and has the following structural formula:



Chemical Formula: $C_{20}H_{24}O_2$
 Molecular Weight: 296.41

CAS number

57-63-6

Ethinylestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils and aqueous solutions of alkali hydroxides.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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10 DATE OF REVISION

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Summary table of changes

Section changed	Summary of new information
Whole document	Reformatted into SmPC format
4.2	'How to delay a period' section updated

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