

PRODUCT INFORMATION

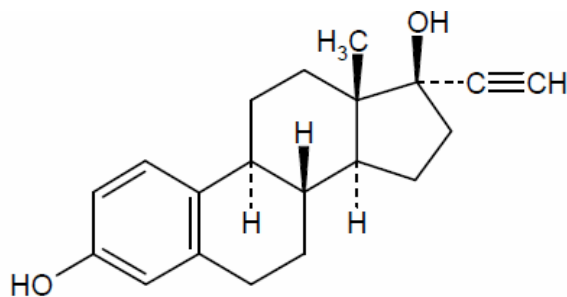
Isabelle 3mg/30µg Tablets

Drospirenone and Ethinyloestradiol

NAME OF THE MEDICINE

Isabelle is a combined oral contraceptive tablet containing the synthetic progestogen, drospirenone and the synthetic oestrogen, ethinyloestradiol.

Ethinyloestradiol is an oestrogen. Chemically, ethinyloestradiol is 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3, 17 β -diol and has the following structural formula:

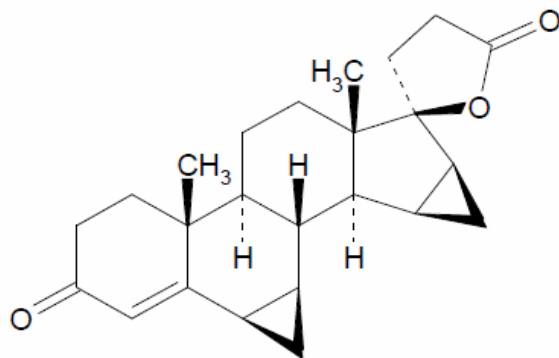


Chemical Formula: $C_{20}H_{24}O_2$

Molecular Weight: 296.41

CAS No: 57-63-6

Drospirenone is a progestogen. The chemical name for drospirenone is 3-oxo-6 α , 7 α , 15 α , 16 α -tetrahydro-3'H,3''H-dicycpropa[6,7:15,16]-17 α -pregn-4-en-21,17-carbolactone and has the following structural formula:



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

Molecular weight: 366.50

CAS No: 67392-87-4

DESCRIPTION

Ethinylestradiol is a white or slightly yellowish-white, crystalline powder. It is practically insoluble in water, freely soluble in ethanol (96 per cent). It dissolves in dilute alkaline solutions.

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.

Each yellow active tablet contains drospirenone 3 mg and ethinylestradiol 30 µg and the excipients: lactose, maize starch, pregelatinised maize starch, magnesium stearate and Opadry Complete Film Coating System 03F82726 Yellow (containing hypromellose, macrogol 6000, purified talc, titanium dioxide and iron oxide yellow).

Each white inactive tablet contains lactose, maize starch, pregelatinised maize starch, magnesium stearate and Opadry Complete Film Coating System 03B28796 White (containing hypromellose, macrogol 400 and titanium dioxide).

PHARMACOLOGY

Pharmacodynamic properties

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 Warnings, Adverse 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 oestrogen-related sodium retention. In combination with ethinyloestradiol, drospirenone displays a favourable lipid profile with an increase in HDL. Drospirenone exerts antiandrogenic activity.

Drospirenone does not counteract the ethinyloestradiol-related sex hormone binding globulin (SHBG) increase which is useful for binding and inactivating the endogenous androgens.

Drospirenone is devoid of any androgenic, oestrogenic, glucocorticoid, and antiglucocorticoid activity. This, in combination with the antimineralocorticoid and antiandrogenic properties, gives drospirenone a biochemical and pharmacological profile closely resembling the natural hormone progesterone. Apart from this, with the higher-dosed combined oral contraceptives (COCs) (50 µg ethinyloestradiol), 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 drospirenone/ethinyloestradiol (3 mg/30 µg) remains to be confirmed.

Pharmacokinetics

Bioavailability studies have been conducted with drospirenone/ethinyloestradiol (3 mg/30 µg).

- 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 about 1 to 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 *sex hormone binding globulin* (SHBG) or corticoid binding globulin (CBG). Only 3 - 5% of the total serum drug concentrations are present as free steroid. The ethinyloestradiol-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-sulphate, both of which are formed without involvement of the P450 system. Drospirenone is metabolised 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*.

Elimination

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 about 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is about 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.

- Ethinyloestradiol

Absorption

Orally administered ethinyloestradiol is absorbed rapidly and completely. Peak serum concentrations of about 88 to 100 pg/mL are reached within 1 to 2 hours after single oral administration. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%. Concomitant intake of food had a variable effect. The maximum concentration was reduced in all subjects and the bioavailability of ethinyloestradiol was reduced in about 25% of the investigated subjects.

Distribution

Serum ethinyloestradiol levels decrease in two phases, the terminal disposition phase is characterised by a half-life of approximately 24 hours. Ethinyloestradiol is highly but nonspecifically bound to serum albumin (approximately 98.5%), and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 L/kg was determined.

Metabolism

Ethinyloestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinyloestradiol 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 sulfate. The metabolic clearance rate of ethinyloestradiol is about 5 mL/min/kg.

Elimination

Ethinyloestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinyloestradiol are excreted at a urinary to biliary ratio of 4:6. The half life of metabolite excretion is about 1 day.

Steady-state conditions

Steady-state conditions are reached during the second half of a treatment cycle and serum levels of ethinyloestradiol accumulate by a factor of about 1.4 to 2.1.

CLINICAL TRIALS

2,274 women have received drospirenone/ethinyloestradiol 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 ethinyloestradiol 30 µg) was 0.43 and 0.09 respectively. The results for both preparations were comparable to the range known for other low dosed OCs containing 30 µg ethinyloestradiol.

For drospirenone/ethinyloestradiol treated women the probability of becoming pregnant for the time of continuous use was estimated. After 2 years of drospirenone/ethinyloestradiol 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 drospirenone/ethinyloestradiol. 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.

Drospirenone/ethinylloestradiol 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 (ethinylloestradiol 30 µg and drospirenone 3 mg) and 822 women on Marvelon (ethinylloestradiol 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 – 0.489 kg and Marvelon +0.019 kg. This difference between the two groups was statistically significant in both studies. Blood pressure was measured in all clinical studies at regular intervals. Drospirenone/ethinylloestradiol had no adverse effect on blood pressure.

INDICATIONS

Isabelle is indicated for use as an oral contraceptive.

CONTRAINDICATIONS

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately.

- Presence or a history of venous or arterial thrombotic/ thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident).
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see under Precautions).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.

PRECAUTIONS

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

- Circulatory Disorders

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

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. The risk for venous thromboembolism is highest during the first year a woman ever uses a COC.

A recently conducted, large (approximately 140,000 women years (WY) of observation), prospective, multinational, cohort study on the safety of OC use, the EURAS study¹ found that the VTE incidence in women with or without other risk factors for VTE who used ethinylloestradiol/drospirenone 30 µg/3 mg were in the same range as that for users of other low dose oestrogen COCs.

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.

Another recently conducted large population based study² 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 the new 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.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of venous (includes pulmonary embolism (PE) and deep venous thrombosis (DVT)) or arterial thrombotic/thromboembolic (includes myocardial infarction (MI), vascular occlusion and cerebrovascular accident) events can include: unilateral leg pain and/or swelling; pain or tenderness in the leg which may be felt only when standing or walking; increased warmth in the affected leg; red or discoloured skin on the leg; sudden severe pain in the chest which may increase with deep breathing; pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe, prolonged headache with no known cause; sudden partial or complete loss of vision; diplopia; sense of anxiety; slurred speech or aphasia; sudden confusion; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Arterial thromboembolic events may be fatal.

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

- age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
- obesity (body mass index over 30 kg/m²);
- dyslipoproteinaemia;
- hypertension;
- migraine
- valvular heart disease;
- atrial fibrillation;
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

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

The increased risk of thromboembolism in the puerperium must be considered.

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

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC use.

- Tumours

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects,^{3,4,5,6} e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users^{7,8}.

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.

- 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 pre-treatment 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 ethinyloestradiol-induced increases in blood pressure observed in normotensive women using other combined oral contraceptives. 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 uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angio-oedema exogenous oestrogens may induce or exacerbate symptoms of angio-oedema.

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 50 µg ethinyloestradiol). 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 yellow active tablet contains 66.17 mg of lactose and each white placebo tablet contains 69.20 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

- Check the following before use:

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of 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 Diseases including HIV infections and AIDS

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

Reduced efficacy

The efficacy of COCs may be reduced in the event of missed tablets, gastro-intestinal disturbances during active tablet taking or concomitant medication (see Dosage and Administration).

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 Pregnancy

Pregnancy Category B3

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

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

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy. Isabelle should not be used during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of Isabelle, the preparation must be discontinued immediately. See also CONTRAINDICATIONS.

Use in Lactation

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

Paediatric Use

Isabelle is only indicated after menarche.

Use in the Elderly

Isabelle is not indicated after menopause.

Patients with hepatic impairment

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

Patients with renal impairment

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

Carcinogenicity

Long-term carcinogenicity studies were performed in mice and rats with drospirenone, ethinyloestradiol 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) greater than that anticipated in humans at the recommended clinical dose. In contrast, treatment with the combination of drospirenone and ethinyloestradiol 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 ethinyloestradiol alone, indicating that ethinyloestradiol was responsible for the increase in neoplastic lesions. Co-administration

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

The ethinyloestradiol-induced tumours in rodents have previously been seen with other ethinyloestradiol-containing products, and are considered attributable to species-specific effects of oestrogens 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 ethinyloestradiol, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

Genotoxicity

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*.

Effect 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.

Effect on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

Interactions with other medicines

- Interactions

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

Hepatic metabolism:

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine and rifampicin; and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort (*Hypericum perforatum*))

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

Interference with Enterohepatic Circulation:

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

Women on treatment with any of these medicines should temporarily use a barrier method in addition to the COC, or choose another method of contraception.

With microsomal enzyme-inducing medicines, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier

method is used runs beyond the end of the active tablets in the COC pack, the placebo tablets should be omitted and the next COC pack started.

The main metabolites of drospirenone in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

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

- Influence of drospirenone/ethinyloestradiol (3 mg/30 µg) on other medications

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

- Other interactions

There is a theoretical potential for an increase in serum potassium in women taking Isabelle 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.

ADVERSE EFFECTS

The most serious adverse reactions associated with the use of oral contraceptives are indicated under PRECAUTIONS.

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 drospirenone/ethinylloestradiol (3 mg/30 µg).

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

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, pain, secretion, enlargement; headache; migraine; changes in libido; depressive moods, mood altered; contact lens intolerance; nausea; vomiting; other gastro-

intestinal complaints (abdominal pain, diarrhoea); changes in vaginal secretion; various skin disorders (e.g rash, urticaria, erythema nodosum, erythema multiforme); fluid retention; change in body weight; hypersensitivity reaction.

In women with hereditary angio-oedema exogenous oestrogens may induce or exacerbate symptoms of angio-oedema.

DOSAGE AND 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 to 3 after starting the placebo tablets (white tablets) and may not have finished before the next pack is started.

How to start Isabelle

- No preceding hormonal contraceptive use (in the past month).

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). The women should be instructed to take a yellow active tablet from the pink 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 to 5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

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

The woman should start with Isabelle preferably on the day after the last active tablet (the last tablet containing the active substances) 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 using Isabelle preferably on the day of removal, but at the latest when the next application would have been due. Isabelle should be started by taking a yellow active tablet from the pack.

- Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier 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, 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 *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 active tablets:

If the user is less than 12 hours late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

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

1. Tablet-taking must never be discontinued for longer than 7 days.
2. Seven days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

- Week 1

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the placebo tablet phase the higher the risk of a pregnancy.

- Week 2

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time.

Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- Week 3

The risk of reduced reliability is imminent because of the forthcoming placebo tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there would be no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until all the active tablets are used up. The 7 tablets from the last row (placebo tablets) 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 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 to 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 delay a period

To delay a period the woman should continue with another pack of Isabelle without taking the 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 the woman may experience breakthrough-bleeding or spotting. Regular intake of Isabelle is then resumed with the next pack.

OVERDOSAGE

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

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Isabelle tablets are contained in blister packs. Each blister contains 21 yellow coloured, round, biconvex, film coated tablets, debossed with 'DR2' on one side and plain on the other side, containing drospirenone 3 mg and ethinyloestradiol 30 µg, followed by 7 white to off-white coloured, round, biconvex, film coated placebo tablets plain on both sides.

Carton containing memo packs of either 1 x 28, 2 x 28, 3 x 28 or 4 x 28 tablets.

Not all pack sizes may be marketed.

Store below 25°C.

NAME AND ADDRESS OF SPONSOR

Supplier

Lupin Australia Pty Ltd
Skipping Girl Place, Suite 6,
651 Victoria Street, Abbotsford,
Victoria 3067
Australia

Distributor

Generic Health Pty Ltd
Suite 1, 1175 Toorak Road,
Camberwell VIC 3124
Australia

POISON SCHEDULE OF THE MEDICINE

S4

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS (THE ARTG)**

DATE OF MOST RECENT AMENDMENT

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