AUSTRALIAN PRODUCT INFORMATION

MARVELON® 28

(desogestrel, ethinylestradiol) Tablets

1 NAME OF THE MEDICINE

Desogestrel and ethinylestradiol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pack contains 21 active tablets each containing 150 micrograms desogestrel and 30 micrograms ethinylestradiol and 7 inert (placebo) tablets.

Excipients with known effect:

- Lactose

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

3 PHARMACEUTICAL FORM

Marvelon 28 has:

21 large, white, round, biconvex tablets coded TR5 on one side, and Organon and a star on the other; and

7 small, white, round, biconvex tablets coded KH2 on one side and a square on the other. These tablets do not contain active ingredients.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oral contraception.

4.2 DOSE AND METHOD OF ADMINISTRATION

How to take Marvelon® 28

One tablet is to be taken daily. The tablets must be taken in the order directed on the package at about the same time each day, with some liquid as needed. Daily tablet taking should be continuous, starting with the tablet marked with the corresponding day from the green zone. Each subsequent pack is to be started immediately following the last placebo (small) tablet. During the placebo days a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last active (large) tablet and may not have finished before the next pack is started.

How to start taking Marvelon® 28

The tablets are taken starting with the tablet marked with the corresponding day from the green zone of the pack. This way, the woman will virtually always have a menstruation-free weekend.

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). If the woman starts on a Thursday or Friday (although these tablets are in the green zone, they are inactive tablets), additional contraceptive precautions are necessary for the first 7 days of active tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch)

The woman should start with Marvelon 28 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 interval or following the last placebo tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Marvelon 28 preferably on the day of removal, but at the latest when the next application would have been due.

The hormone-free interval of the previous method should never be extended beyond its recommended length.

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 in all of these cases should be advised to additionally use a barrier method for the first 7 days of active tablet-taking.

Following a first trimester abortion

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

After childbirth or a second or third trimester abortion

For breastfeeding women see **Section 4.6 Fertility, Pregnancy and Lactation, Use in lactation**.

Women should be advised to start 21 to 28 days after delivery or second-trimester abortion (no later than day 26 if starting on a Thursday or day 27 if starting on a Friday). When starting later than day 28, the woman should be advised to additionally use a barrier method for the first 7 days of active 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. The increased risk of VTE during the postpartum period should be considered when restarting Marvelon 28 (see **Section 4.6 Fertility, Pregnancy and Lactation, Use in pregnancy**).

Management of missed tablets

When Marvelon is taken according to the directions for use, the occurrence of pregnancy is highly unlikely. However, the reliability of oral contraceptives may be reduced under the following circumstances:

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 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. 7 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:

If the user is more than 12 hours late in taking any large tablet (or several large tablets) from the pack, she should take the last forgotten tablet, even if this means taking two tablets in one day, and then continue to take tablets at the normal time. Additional contraceptive precautions should be taken for the next 7 days.

If these 7 days would usually include the taking of small (inert) tablets, the large (active) tablets of the next pack should be started as soon as the large tablets from the current pack are finished. This prevents an extended break in taking active tablets, which may increase the risk of the ovaries releasing an egg and thus reducing contraceptive protection. The woman will not have a period until the end of the second pack of tablets, but this is not harmful, nor does it matter if she experiences some bleeding on the days she is taking Marvelon.

Whenever large tablets are missed at the beginning of the pack (that is, missing one or more of the first 7 large tablets), and sexual intercourse has taken place, the possibility of pregnancy should be considered.

Advice in case of gastro-intestinal disturbances

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

If vomiting occurs within 3-4 hours after tablet taking, the advice concerning missed tablets, as given previously, 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.

Additional contraceptive precautions

When additional contraceptive precautions are required the woman should be advised either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the Pill disrupts the cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

How to shift periods or how to delay a period

To delay a period the woman should continue with another pack of Marvelon 28 without having a placebo tablet interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Marvelon 28 is then resumed after the usual 7-day placebo tablet interval.

To shift her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

4.3 CONTRAINDICATIONS

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during the use of MARVELON, 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, hyperhomocysteinaemia and antiphospholipid-antibodies.
    - 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), APC-resistance (including factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency;
    - 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 hypertriglyceridaemia
- Presence or history of severe hepatic disease as long as liver function have not returned to normal
- 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 MARVELON

Marvelon 28 is contraindicated for use with the Hepatitis C virus combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **Section 4.4 Special Warnings and Precautions for Use**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If any of the conditions/risk factors mentioned below is present, the benefits of the use of MARVELON should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using MARVELON. 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 its use should be discontinued.

1. Circulatory disorders

Risk of venous thromboembolism (VTE)

Epidemiological studies have shown an association between the use of combined oral contraceptives (COCs) containing ethinylestradiol and an increased risk of venous thrombotic and thromboembolic diseases such as deep venous thrombosis, and pulmonary embolism. These events occur rarely in average-risk women.

The use of any ethinylestradiol-containing COC is associated with an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The risk is also increased after initially starting a COC or restarting the same or different COC after a break in use of 4 weeks or more. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 5 to 20 per 10,000 pregnant woman years. This compares with 1 to 5 cases per 10,000 woman-years for non-users. VTE is fatal in 1%-2% of cases.

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

The use of any CHC increases the risk of VTE compared with no use.

The risk of VTE with the COC is greatest for products containing over 50 µg of ethinylestradiol. There is less risk for products containing less than 35 µg ethinylestradiol. MARVELON contains the progestogen desogestrel which has an increased risk of VTE compared to other progestogens such as levonorgestrel, norgestimate or norethisterone which are associated with the lowest risk of VTE (see table below).

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

Table 1

Risk[1] of developing a blood clot (VTE) in a year

Women not using a combined hormonal contraceptive (CHC) and not pregnant	About 1-5 out of 10,000 women[1]
Women using a CHC containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000 women
Women using a CHC containing etonogestrel or norelgestromin	About 6-12 out of 10,000 women
Women using a CHC containing drospirenone, gestodene, desogestrel or cyproterone acetate	About 9-12 out of 10,000 women
Women using a CHC containing chlormadinone acetate	Not yet known[3]
Women using a CHC containing dienogest and estradiol valerate or nomegestrol acetate and E2	Not yet known[3]

[1] In any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

[2] While cyproterone acetate is indicated for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of VTE associated with cyproterone acetate use is considered to be 1.5 to 2 times higher than for CHCs containing levonorgestrel.

[3] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products. Where the risk for a particular progestogen is uncertain, the risk of the class should be used in determining the risk for the individual patient.

The increased risk of VTE during the postpartum period should be considered if re-starting MARVELON (see **Section 4.2 Dose and Method of Administration**).

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

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

Risk factors for VTE

- Obesity (body mass index over 30 kg/m^2). 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: Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- Other medical conditions associated with VTE:
    - 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 MARVELON (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 MARVELON has not been discontinued in advance.

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

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

Symptoms of VTE (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 COC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or
- walking,
- increased warmth in the affected leg;
- red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

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

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

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

Risk of arterial thromboembolism (ATE)

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

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

Risk factors for ATE

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity (BMI over 30 kg/m^2)
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant), Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency.
- Migraine
- Other medical conditions associated with adverse vascular events:
    - Diabetes mellitus
    - Valvular heart disease
    - Atrial fibrillation

- Dyslipoproteinaemia
- Systemic lupus erythematosus

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

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

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

Symptoms of ATE

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

Symptoms of a stroke can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- 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.

2. Neoplasms

- Several epidemiological studies suggest that use of combined oral contraceptives, in particular if used for 5 years or longer, has been associated with an increased risk of cervical intra-epithelial neoplasia or invasive cervical cancer. After cessation of use of oral contraceptives the risk gradually decreases over time to that of non-users in about 8 years. Human papilloma virus is believed to be the most important cause of cervical cancer, but the independent association with the use of hormonal contraceptives suggests a contributing effect. These findings must be balanced against evidence of significant effects attributable to sexual behaviour, smoking, parity and other factors. Refer to **Section 4.4 Special Warnings and Precautions for Use, Medical examination/consultation**.
- An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

- 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. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
- In another epidemiological study of 1.8 million Danish women followed an average of 10.9 years, the reported RR of breast cancer among COC users increased with longer duration of use compared with women who never used COCs (overall RR = 1.19; RR ranged from 1.17 for 1 to less than 5 years of use to 1.46 after more than 10 years of use). The reported absolute risk difference (number of breast cancer cases between never-users compared with current and recent COC users) was small: 13 per 100,000 woman- years.
- Epidemiological 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.
- 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 hepatic 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.

(See also **Section 5.3 Preclinical Safety Data, Genotoxicity/ carcinogenicity**.)

3. Hepatitis C

- During clinical trials with the HCV combination drug regimen ombitasvir/ paritaprevir/ ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. Marvelon 28 must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **Section 4.3 Contraindications** and **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**). Marvelon 28 can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

4. Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
- The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss; (hereditary) angioedema.

- 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 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.
- Marvelon 28 contains < 80 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on lactose-free diet should take this amount into consideration.

When counselling the choice of contraceptive method(s), all the above information should be taken into account.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the **Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use**, and should be repeated periodically during the use of COCs. In general, an annual examination is recommended. 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 based on established guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology. Women who have ever been sexually active, including current and past users of hormonal contraceptives, should have scheduled Pap smear examinations in accordance with current public health guidelines.

Women should be advised that Marvelon does not protect against sexually transmitted diseases (STDs), including HIV infections (AIDS) and Human Papilloma Virus [HPV]. The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs, but that even barrier contraceptives may not protect against HPV.

Reduced efficacy

The efficacy of Marvelon 28 may be reduced in the event of missed active tablets, gastrointestinal disturbances during active tablet taking or concomitant medications that decrease the plasma concentration of etonogestrel, the active metabolite of desogestrel.

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 interval. 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

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.

See Section **4.3 Contraindications**

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

See Section **4.5 Interactions with Other Medicines and Other Forms of Interactions, Effects on laboratory tests**

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

Hepatic metabolism: Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of combined oral contraceptives, including Marvelon 28. These products include phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, rifabutin and possibly also oxycarbazepine, topiramate, felbamate, griseofulvin, some HIV protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz) and products containing the herbal remedy St. John's Wort.

Enzyme induction can occur after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After drug therapy is discontinued enzyme induction can last for about 28 days.

When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g. nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g. boceprevir, telaprevir), can increase or decrease plasma concentrations of progestins, including etonogestrel, the active metabolite of desogestrel, or estrogens. The net effect of these changes may be clinically relevant in some cases.

Women receiving any of the above mentioned hepatic enzyme-inducing medicinal or herbal products should be advised that the efficacy of Marvelon 28 may be reduced. A barrier contraceptive method should be used in addition to Marvelon 28 during administration of the hepatic enzyme inducing medicinal product, and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product.

If concomitant drug administration runs beyond the end of the active tablets in the current COC pack, the next COC pack should be started right away without the usual placebo tablet interval.

For women on long-term therapy with enzyme-inducing medicinal products an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP 3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel, the active metabolite of desogestrel.

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

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. Marvelon 28 must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **Section 4.3 Contraindications** and **Section 4.4 Special Warnings and Precautions for Use**). Marvelon 28 can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See Section 5.1 Pharmacodynamic Properties.

Use in pregnancy

(Category B3)

Marvelon is contraindicated during pregnancy. If pregnancy occurs during treatment with Marvelon, further intake should be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

In animal studies, maternal administration of high doses of estrogens has produced urogenital malformations in the offspring. The relevance of the animal findings for the clinical use of ethinylestradiol is not certain. However, there was no evidence for teratogenic activity when ethinylestradiol/desogestrel was given orally to pregnant rats (up to 0.2/0.5 mg/kg) or rabbits (0.04/0.1 mg/kg) during organogenesis. These doses correspond to exposure levels (based on body surface area) 15 to 60 times human exposure at the maximum recommended dose. The combination had no adverse peri/post natal effects in rats at similarly high exposure levels.

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 with the milk but there is no evidence that this adversely affects infant health.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Various adverse reactions have been associated with oral contraceptive use. The most serious reactions associated with the use of oral contraceptives are dealt with under **Section 4.4 Special Warnings and Precautions for Use** (see also **Section 4.3 Contraindications**).

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 its use should be discontinued.

Possibly related undesirable effects that have been reported in clinical trials or observational studies with Marvelon 28 or CHC users in general are listed in the Table below:

Table 2

System Organ Class	Common (> 1/100)	Uncommon (> 1/1000 and < 1/100)	Rare (< 1/1000)
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders	Depressed mood, mood altered	Libido decreased	Libido increased
Nervous system disorders	Headache	Migraine	
Eye disorders			Contact lens intolerance, cataract
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Skin and subcutaneous tissue disorders		Rash, urticaria	Erythema nodosum, erythema multiforme, hirsutism, acne, alopecia
Reproductive system and breast disorders	Breast pain, breast tenderness	Breast enlargement	Vaginal discharge, breast discharge
Investigations	Weight increased		Weight decreased

The most appropriate MedDRA term (version 11.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

A number of undesirable effects have been reported in women using combined oral contraceptives, which are discussed in more detail in **Section 4.3 Special Warnings and Precautions for Use**. These include: venous thromboembolic disorders; arterial

thromboembolic disorders; hypertension; hormone-dependent tumours (e.g. liver tumours, breast cancer); chloasma.

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 atwww.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The contraceptive effect of COCs is based on the interaction of various factors. The primary mechanisms are inhibition of ovulation (by suppression of gonadotropins) and changes in the cervical secretion (blocking the entry of sperm into the uterus). Besides protection against pregnancy, COCs have several positive properties which, next to the negative properties (see **Section 4.4 Special Warnings and Precautions for Use**, **Section 4.8 Adverse Effects (Undesirable Effects)**), can be useful in deciding on the method of birth control. For the majority of users, the cycle is more regular, the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dosed (0.050 mg ethinylestradiol) COCs have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

Receptor binding studies as well as studies in animals and humans have shown that etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with low intrinsic androgenicity. As a result, desogestrel in Marvelon does not counteract the estrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

DESOGESTREL

Absorption

After oral dosing of Marvelon, desogestrel is rapidly absorbed and converted to 3-keto-desogestrel (etonogestrel). Peak serum concentrations of approximately 2 ng/mL are reached after 1.5h after single ingestion and absolute bioavailability is 62 - 81%.

Distribution

Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 – 4 % of the total serum drug concentrations are present as free steroid, 40 - 70% are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution over the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of desogestrel is 1.5 L/kg.

Metabolism

Etonogestrel is completely metabolised by the known pathways of steroid metabolism. The metabolic clearance rate from serum is about 2mL/min/kg. No interaction was found when co-administered with ethinylestradiol.

Excretion

Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted at a urinary to biliary ratio of about 6:4.

Steady-state conditions: Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about two- to threefold, reaching steady state conditions during the second half of the treatment cycle.

ETHINYLESTRADIOL

Absorption

Orally administered ethinylestradiol is rapidly and almost completely absorbed. Peak serum concentrations of about 80 pg/mL are reached within 1-2 hours. Absolute bioavailability, as a result of presystemic conjugation and first pass metabolism, is approximately 60%.

Distribution

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 about 5L/kg was determined.

Metabolism

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

Excretion

Ethinylestradiol serum levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Unchanged drug is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions: Steady state concentrations are reached after 3-4 days when serum drug levels are higher by 30 - 40% as compared to single dose.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Assays for gene mutations *(*S. typhimurium*)* and chromosomal damage (in vivo mouse micronucleus test) performed with desogestrel or the combination did not provide any evidence of a genotoxic potential.

Carcinogenicity

Carcinogenicity studies for human risk estimation were performed for both components of the preparation, ethinylestradiol and desogestrel, and the combination.

Long-term studies with ethinylestradiol/desogestrel in rats and mice at oral doses up to 0.2/0.5 mg/kg elicited an increased incidence of pituitary and mammary gland tumours. The tumours occurred at exposure levels (based on body surface area) 30 to 60 times human exposure at the maximum recommended dose. The mechanism involved estrogen- and prolactin-sensitive pathways in rodents. These pathways have no direct counterpart in humans, therefore the clinical significance of these findings is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Active tablets: potato starch, povidone, stearic acid, colloidal anhydrous silica, dl-alpha-tocopherol, lactose monohydrate.

Inert tablets: potato starch, magnesium stearate and lactose monohydrate.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C and protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack of Marvelon (28 day pack), AUST R42894, consists of push-through strips with: 21 large, white, round, biconvex tablets and 7 small, white, round, biconvex tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

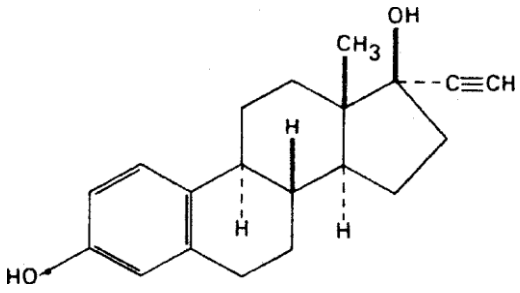
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Marvelon is a combined oral contraceptive (COC) preparation containing the estrogen ethinylestradiol and the progestagen desogestrel as the active substances.

Chemical structure

Ethinylestradiol:

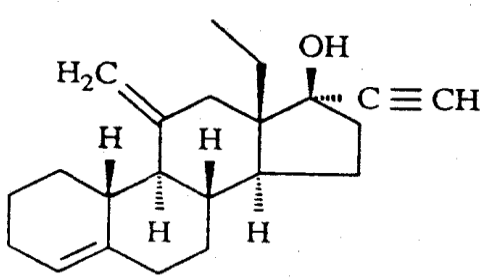


Chemical Name: 19-nor-17a-pregna-1,3,5,(10)-triene-20-yne-3,17b-diol.

Molecular Formula: $C_{20}H_{24}O_2$. Molecular mass: 296.4.

Ethinylestradiol: a white or slightly yellowish white crystalline powder. Melting Point: 181-185°C. It is practically insoluble in water, freely soluble in ethanol (96%) and in ether, sparingly soluble in chloroform. It dissolves in dilute alkaline solutions.

Desogestrel:



Chemical name: 13β-Ethyl-11-methylene-18, 19-dinor-17α-pregn-4-en-20-yn-17β-ol.

Molecular Formula: $C_{22}H_{30}O$. Molecular mass: 310.5.

Desogestrel: a crystalline powder, it is a progestogen, semi synthetically produced from naturally occurring plant steroids. It is optically pure, is practically insoluble in water, and slightly soluble in ethanol and ethylacetate.

CAS Number

Ethinylestradiol: 57-63-6

Desogestrel: 54024-22-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Organon Pharma Pty Limited
Building A, 26 Talavera Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

16 December 1992

10 DATE OF REVISION

16 February 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat of PI
8	Amend Sponsor Details due to transfer of sponsorship