SCHEDULING STATUS

S3

1. NAME OF MEDICINE

MARVELON® 150/30 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 larger white tablets containing 0,15 mg desogestrel and 0,03 mg ethinylestradiol per tablet.

7 smaller white tablets that do not contain any active ingredients (placebo tablets).

Contains sugar: lactose (< 80 mg)

For full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

MARVELON 150/30 consists of two types of tablets distinguished by mark and size. The 21 larger white tablets contain the active ingredients and are round and biconvex. They have bevelled edges, coded ORGANON and a star on one side and the tablet code TR above 5 on the reverse side. The 7 smaller white tablets are round and flat with bevelled edges coded KH above 2 on one side and a square on the reverse side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Oral contraception.

4.2 Posology and method of administration

How to take MARVELON 150/30

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 28 consecutive days. The

first tablet should be taken from the blister in the green section of the calendar pack marked with the appropriate day of the week. Each subsequent pack is started the day after the last tablet of the current pack. During the placebo days a withdrawal bleed usually occurs. This usually starts on day 2 to 3 after the last active tablet and may not have finished before the next pack is started.

How to start MARVELON 150/30

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). 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 another combined oral contraceptive

The woman should start with MARVELON 150/30 on the day after the last active tablet of her previous combined oral contraceptive but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous combined oral contraceptive.

Changing from a progestogen-only-method (mini pill, injection, implant)

The woman may switch any day from the mini pill (from an implant 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 use a barrier method additionally for the first 7 days of tablet-taking.

Following first-trimester abortion

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

Following delivery or second-trimester abortion

For breastfeeding women see section 4.6.

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 use a barrier method additionally for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of combined oral contraceptive 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 150/30 (see section 4.4).

Management of Missed 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 active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

- “active tablet”-taking must never be discontinued for longer than 7 days.
- 7 days of uninterrupted “active tablet”-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Due to the green starting zone, the first cycle of active tablets can be shorter than subsequent cycles. If tablets are missed in the first cycle of use, the medical practitioner is referred to the basic rules. In all other cases, in accordance with these rules, the following **advice can be given in daily practice:**

- **Week 1 (active tablets)**

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 regular placebo tablet interval, the higher the risk of a pregnancy.

- **Week 2 (active tablets)**

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 one tablet, the woman should be advised to use extra precautions for 7 days.

- **Week 3 (active tablets)**

The risk of reduced reliability is imminent because of the forthcoming placebo tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore, 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. The next pack must be started as soon as the active tablets in the current pack are finished, i.e., no placebo tablets (smaller tablets, marked on the pack with a red circle) should be taken. The user is unlikely to have a withdrawal bleed until the end of the second pack but she may experience spotting or breakthrough bleeding on “active tablet”-taking days.
2. The woman may also be advised to discontinue “active tablet”-taking from the current pack. She should then immediately continue with the placebo tablets. The total number

of missed tablets and placebo tablets must never exceed seven tablets. Subsequently she should continue with the next pack.

- **Week 4 (placebo tablets)**

Contraceptive protection is not reduced; the woman should take further tablets at the usual time.

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

Advice in case of vomiting

If vomiting occurs within 3 to 4 hours after tablet taking, absorption may not be complete. In such an event the advice concerning missed tablets, as given in the previous section, 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 MARVELON 150/30 without having a placebo tablet interval (from the section indicated with the red rings). 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 150/30 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 time 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).

Reduced cycle control

With all combined oral contraceptives, 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 combined oral contraceptive has been taken according to the directions described above, it is unlikely that the woman is pregnant. However, if the combined oral contraceptive 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 combined oral contraceptive use is continued.

4.3 Contraindications

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

- Presence or history of venous thrombosis (e.g., deep venous thrombosis, pulmonary embolism).
- Presence or history of arterial thrombosis (e.g., myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g., transient ischaemic attack, angina pectoris).
- Known predisposition for venous or arterial thrombosis, such as Activated Protein C (APC) resistance, anti-thrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antipospholipid antibodies.

- The presence of a serious or multiple risk factors for venous or arterial thrombosis (such as e.g., hypertension, a family history of thromboembolic events, prolonged immobilisation (see section 4.4).
- Major surgery with prolonged immobolisation (see section 4.4).
- History of migraine associated with focal neurological symptoms (see section 4.4).
- Presence or history of hepatic disease as long as liver function values 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.
- Diabetes mellitus with vascular involvement.
- Hypersensitivity to any of the active or inactive ingredients of MARVELON 150/30.

MARVELON 150/30 is contraindicated for use with the Hepatitis C virus combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section 4.4).

4.4 Special warnings and precautions for use

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

If any of the conditions/risk factors mentioned below is present, the benefits of combined hormonal contraceptive 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 case of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her medical practitioner. The medical practitioner should then decide on whether use of MARVELON 150/30 should be discontinued.

Throughout this section the general term combined hormonal contraceptive (CHC) is used when data exist for oral and non-oral contraceptives. The term combined oral contraceptive (COC) is used when data exist only for oral contraceptives.

1. Circulatory Disorders

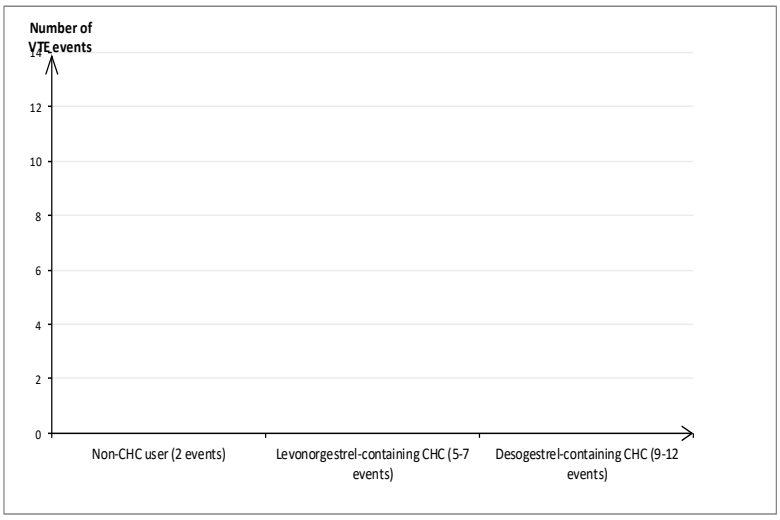
- Epidemiological studies have shown an association between the use of combined hormonal contraceptives such as MARVELON 150/30 and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism.
- The use of combined hormonal contraceptives such as MARVELON 150/30 is associated with an increased risk of venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, which may occur during the use of combined hormonal contraceptives. The risk is highest during the first year a woman ever uses a combined hormonal contraceptive. This risk is also increased after initially starting a combined hormonal contraceptive or restarting the same or different combined hormonal contraceptive after a break in use of 4 weeks or more.
- In women who do not use a CHC and are not pregnant about 2 out of 10 000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated that out of 10 000 women who use a CHC containing desogestrel between 9 and 12 women will develop a VTE in one year; this compares with about 62 in women who use a levonorgestrel-containing CHC.

In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

- VTE may be fatal in 1 – 2 % of cases.

Number of VTE events per 10,000 women in one year



[1]These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.

[2]Mid-point of range of 5 - 7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2,3 to 3,6.

- Thrombosis has been reported to occur in other blood vessels e.g., hepatic, mesenteric, renal or retinal veins and arteries, in combined hormonal contraceptive users.
- Symptoms of venous or arterial thrombosis can include: Unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; 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.

The risk of venous thromboembolism increases with:

- Increasing age;
- A positive family history (i.e., venous thromboembolism, even 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 combined oral contraceptive use;
- Obesity (Body mass index over 30 kg/m^2);
- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue combined oral contraceptive use (in the case of elective surgery, at least 4 weeks in advance) and not to resume until 2 weeks after complete remobilisation (see section 4.3);
- Possible with superficial thromobophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the aetiology of venous thromboembolism;
- In the immediate post-partum period.

The risk of arterial thromboembolic complications increases with:

- Increasing age;
- Smoking (with a combination of heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- Dyslipoproteinaemia;
- Obesity (body mass index over 30 kg/m^2);
- Hypertension;
- Migraine;
- Valvular heart disease;
- Atrial fibrillation;
- A positive family history (i.e., arterial thromboembolism, even 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 combined oral contraceptive use;
- In the immediate post-partum period.

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

The onset of or increase in frequency or severity of migraine during combined oral contraceptive use (which may be prodromal of a cerebrovascular event) is a reason for immediate discontinuation of the combined oral contraceptive.

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

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

2. Tumours

- An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in epidemiological studies.

- A meta-analysis from epidemiological studies reported that there is an increased relative risk of having breast cancer diagnosed in women who are currently using combined oral contraceptives such as MARVELON 150/30.

- 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.

- Benign liver tumours and more rarely, malignant liver tumours, have been reported in users of combined oral contraceptives. 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 combined oral contraceptives.

3. Hepatitis C

- During clinical trials with the HCV combination medicine 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 150/30 must be discontinued prior to starting therapy with the combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section 4.3 and 4.5). MARVELON 150/30 can be restarted approximately 2 weeks following completion of treatment with the combination medicine regimen.

4. Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using combined oral contraceptives.

- Small increases in blood pressure have been reported in many women taking combined oral contraceptives and clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of a combined oral contraceptive then, it is prudent for the medical practitioner to withdraw the combined oral contraceptive and treat the hypertension. Where considered appropriate, combined oral contraceptive use may be resumed if normotensive values can be achieved with antihypertensive therapy.
- The following conditions have been reported to occur or deteriorate with combined oral contraceptive use:
    - 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.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of combined oral contraceptive use until markers of liver function return to normal. Recurrence of cholestatic jaundice that occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of combined oral contraceptives.
- Although combined oral contraceptives 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 combined oral contraceptives. However, diabetic women should be carefully observed while taking combined oral contraceptives.
- Crohn's disease and ulcerative colitis have been associated with combined oral contraceptive 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 combined oral contraceptives.
- Respiratory: Asthma may deteriorate in women using combined oral contraceptives.
- MARVELON 150/30 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 a lactose-free diet should take this amount into consideration.

Medical Examination/Consultation

Prior to the initiation or reinstitution of MARVELON 150/30 a complete medical history including family history and pregnancy must be ruled out. Blood pressure should be measured and if clinically indicated a physical examination should be performed, guided by the **Contraindications** (see section 4.3) and **Special warnings and precautions for use** (see section 4.4). The women should be instructed to carefully read the Patient Information Leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to individual women.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy: The efficacy of MARVELON 150/30 may be reduced in the event of missed tablets (see section 4.2), gastrointestinal disturbances or other concomitant medication that decrease the plasma concentration of etonogestrel, the active metabolite of desogestrel (see 4.5).

4.5 Interaction 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 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 150/30.
These products include phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin and possibly also oxcarbamazepine, 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 medicine 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 oestrogens. 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 150/30 may be reduced. A

barrier contraceptive method should be used in addition to MARVELON 150/30 during administration of the hepatic enzyme-inducing medicinal product, and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product.
If concomitant medicine administration runs beyond the end of the active tablets in the current combined oral contraceptive pack, the next combined oral contraceptive pack should be started right away without the usual placebo tablet interval.

For women on long-term therapy with enzyme-inducing medicines and 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) CYP3A4 inhibitors may increase the serum concentrations of oestrogens or progestins, including etonogestrel, the active metabolite of desogestrel.

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

During clinical trials with the HCV combination medicine 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 150/30 must be discontinued prior to starting therapy with the combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section 4.3 and 4.5). MARVELON 150/30 can be restarted approximately 2 weeks following completion of treatment with the combination medicine regimen.

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 metabolites and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who have used combined oral contraceptives prior to pregnancy, nor a teratogenic effect when combined oral contraceptives were taken inadvertently during early pregnancy. See section 4.3. Feminisation of the male foetus may occur.

Breastfeeding

Lactation may be influenced by combined oral contraceptives, as they may reduce the quantity and change the composition of breast milk therefore, the use of combined oral contraceptives should generally not be recommended until the breastfeeding 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 Machinery

No observed effects.

4.8 Undesirable effects

Possibly related adverse effects that have been reported in clinical trials or observational studies MARVELON 150/30 or combined hormonal contraceptive users in general are listed in the table below[1]

System Organ Class	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1 000 and < 1/100)	Rare (≥ 1/10 000 and < 1/1 000)
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
Vascular disorders			Venous thromboembolism[2], arterial thromboembolism[2]
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Skin and subcutaneous tissue disorders		Rash, urticaria	Erythema nodosum, erythema multiforme
Reproductive system and breast disorders	Breast pain, breast tenderness	Breast enlargement	Vaginal discharge, breast discharge
Investigations	Weight increased		Weight decreased

[1] The most appropriate MEDRA term to describe a certain adverse reaction is listed.

Synonyms or related conditions are not listed but should be taken into account as well.

[2] Incidence is observational cohort studies of ≥ 1/10 000 to < 1/1 000 women-years.

Post marketing reported side effects:

The following side effects have been reported with the post marketing use of oestrogen and/or progesterone/progestogen containing medicines: Severe depression with a higher risk of suicidal thoughts/behaviour and suicide.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://sahpra.org.za/Publications/Index/8.

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 possible slight vaginal bleeding in young girls. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

A.18.8 Ovulation controlling agents

MARVELON 150/30 is an oestrogen/progestogen combination oral contraceptive that inhibits ovulation.

5.1 Pharmacodynamic properties

The contraceptive effect of MARVELON 150/30 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.

5.2 Pharmacokinetic properties

Desogestrel

Absorption

Orally administered desogestrel is well absorbed and converted to etonogestrel. Peak serum concentrations of approximately 2 ng/ml are reached at about 1,5 hours after single ingestion. Bioavailability is 62 to 81 %.

Distribution

Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 to 4 % of the total serum concentrations are present as free steroid, 40 to 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 litre/kg.

Metabolism

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

Elimination

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, 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 well absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1 to 2 hours. Absolute bioavailability as a result of pre-systemic 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 5 litre/kg was determined.

Metabolism

Ethinylestradiol is subject to pre-systemic 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 is about 5 ml/min/kg.

Elimination

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

Steady-state conditions

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients: Colloidal silicon dioxide, lactose, magnesium stearate, potato starch, povidone, stearic acid and dl-alpha-tocopherol. The daily amount of lactose (< 80 mg) is such that women with intolerance to lactose are highly unlikely to experience a problem.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Not applicable

6.4 Special precautions for storage

Store at or below 30 °C. Protect from light and moisture.

Keep out of reach of children.

6.5 Nature and contents of the container

Push-through strips contain 21 active white tablets and 7 smaller white placebo tablets, the latter being circled in red on the strip foil.

6.6 Special precautions for disposal

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor, 22 Magwa Crescent, Gateway West

Waterfall City, Midrand, 2090

South Africa

8. REGISTRATION NUMBER

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