# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Mercilon 150/20 microgram Tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Desogestrel 150 micrograms
Ethinylestradiol 20 micrograms

Also contains approximately 68mg Lactose Monohydrate per tablet.
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.
The tablets are white, round, biconvex and 6mm in diameter. They are coded on one side 'Organon' and an asterix '*' and on the reverse side 'TR' above '4'.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indication

Contraception.

The decision to prescribe Mercilon should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Mercilon compares with other CHCs (see sections 4.3 and 4.4).

### 4.2 Posology and method of administration

**Paediatric population**

The safety and efficacy of Mercilon in adolescents under the age of 18 years have not been studied.

Method of administration: oral use.

Before starting Mercilon, a thorough general medical and gynaecological examination (including breasts and a cytological smear of the cervix) should be carried out and the family medical history carefully noted. Disturbances of the clotting mechanisms should be ruled out if any members of the family have suffered from thromboembolic diseases (e.g. deep vein thrombosis, stroke, myocardial infarction) at a young age.

Pregnancy must be excluded ideally by a pregnancy test.

As a precaution, thorough examinations should be conducted at approximately six month intervals during the use of the tablets.

**How to take Mercilon**

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 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval, during which time a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

**How to start taking Mercilon**

*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 day 2-5 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), vaginal ring or transdermal patch)*
The woman should start with Mercilon preferably on the day after the last active tablet (the last tablet containing the active substance) of her previous CHC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous CHC. In case a vaginal ring or a transdermal patch has been used, the woman should start using Mercilon preferably on the day of removal, but at the latest when the next application would have been due.
Not all contraceptive methods (transdermal patch, vaginal ring) may be marketed in all EU countries.

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

*Following delivery or second-trimester miscarriage*
For breastfeeding women see Section 4.6.
Women should be advised to start at day 21 to 28 after delivery or second trimester miscarriage. 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 CHC use or the woman has to wait for her first menstrual period.

**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 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. 7 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 pill as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of 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 tablet-free 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 the tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e., no gap should be left between packs. 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 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 normal tablet-free interval, the possibility of a pregnancy should be considered.

**Advice on 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 in Section 4.2, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

**How to shift periods or how to delay a period**

Delaying a period is not an indication for the product. However, if in exceptional cases a period needs to be delayed, the woman should continue with another pack of Mercilon without a tablet-free 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 Mercilon is then resumed after the usual 7-day tablet-free 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 tablet-free 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 hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
    - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE]).

    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
    - Major surgery with prolonged immobilisation (see section 4.4).
    - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4).
- Presence or risk of arterial thromboembolism (ATE)
    - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
    - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA).
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
    - History of migraine with focal neurological symptoms.
    - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
        - diabetes mellitus with vascular symptoms
        - severe hypertension
        - severe dyslipoproteinaemia

- Pancreatitis or a history there of if associated with severe hypertriglyceridaemia.
- Presence or history of severe 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 neoplasia (e.g. of the genital organs or the breasts).
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Mercilon is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see sections 4.4 and section 4.5).

## 4.4 Special Warnings and Precautions for Use

**Warnings**

If any of the conditions or risk factors mentioned below is present, the suitability of Mercilon should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Mercilon should be discontinued.

*Conditions which need supervision*

- Risk factors for thrombo-embolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Cholelithiasis, jaundice and/or pruritus related to cholestasis
- Herpes gestationis
- Migraine or (severe) headache

- Systemic lupus erythematosus
- Endogenous depression
- Asthma
- Otosclerosis-related hearing loss
- Porphyria

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 physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

1. Circulatory Disorders

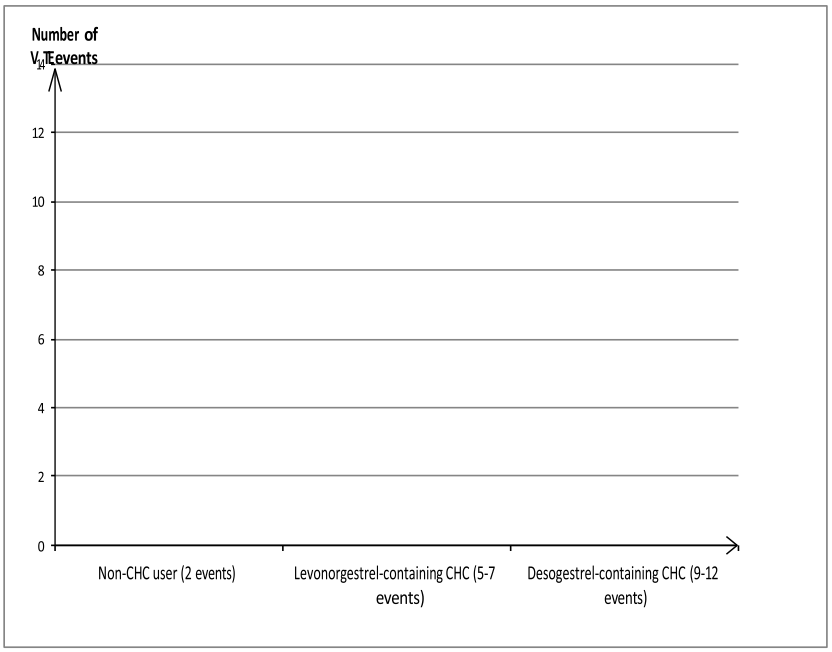
**Risk of venous thromboembolism (VTE)**

- The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Mercilon may have up to twice this level of risk. 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 Mercilon, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started 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[1] 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 6[2] 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.

[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 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

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




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

**Risk factors for VTE**

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

Mercilon is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

**Table: Risk factors for VTE**

| **Risk factor** | **Comment** |
|---|---|
| Obesity (body mass index over 30 kg/m²) | Risk increases substantially as BMI rises.<br>Particularly important to consider if other risk factors also present. |
| Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma<br><br>Note: Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors. | In these situations it is advisable to discontinue use of the patch/pill/ring (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.<br>Antithrombotic treatment should be considered if Mercilon has not been discontinued in advance. |

| | |
|---|---|
| Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. below 50). | If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use. |
| Other medical conditions associated with VTE | Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease |
| Increasing age | Particularly above 35 years |

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6).

**Symptoms of VTE (deep vein thrombosis and pulmonary embolism)**

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

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

Symptoms of pulmonary embolism (PE) can include:

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

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

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

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

**Risk of arterial thromboembolism (ATE)**

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

**Risk factors for ATE**

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Mercilon is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

**Table: Risk factors for ATE**

| **Risk factor** | **Comment** |
|---|---|
| Increasing age | Particularly above 35 years |
| Smoking | Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception. |
| Hypertension | |
| Obesity (body mass index over 30 kg/m$^2$) | Risk increases substantially as BMI increases.<br>Particularly important in women with additional risk factors |
| Positive family history (arterial thromboembolism ever in a sibling or parent especially at a relatively early age e.g. below 50). | If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use. |
| Migraine | An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation. |
| Other medical conditions associated with adverse vascular events | Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus. |

**Symptoms of ATE**

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident 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 Tumours

- Epidemiological studies indicate that the long-term use of oral contraceptives displays a risk factor for the development of cervical cancer in women infected with human papillomavirus (HPV). However, there is still uncertainty about the extent to which this finding is influenced by confounding effects (e.g. differences in number of sexual partners or in 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.

- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of CHCs. In isolated cases, these tumours have led to life threatening intra-abdominal haemorrhage. 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 CHCs.

3. ALT elevations

- During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.5).

4. Other Conditions

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

- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

- 

- Although small increases in blood pressure have been reported in many women taking CHCs, clinically relevant increases are rare. A relationship between CHC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a CHC then it is prudent for the physician to withdraw the CHC and treat the hypertension. Where

considered appropriate, CHC 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 CHC use, but the evidence of an association with CHC use is inconclusive: jaundice and/or pruritis 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 CHC 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 CHCs.

- Although CHCs 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 CHCs. However, diabetic women should be carefully observed while taking CHCs.

- Crohn's disease and of ulcerative colitis has been reported during CHC 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 CHCs.

- Mercilon contains <80mg 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**

Prior to the initiation or reinitiation of Mercilon, a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (see Section 4.3) and warnings (see Section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Mercilon compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.
The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

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

**Reduced efficacy**

The efficacy of Mercilon may be reduced in the event of e.g. missed tablets (Section 4.2), gastro-intestinal disturbances (Section 4.2) or concomitant medications that decrease the plasma concentration of ethinylestradiol and/or etonogestrel, the active metabolite of desogestrel (Section 4.5).

Herbal preparations containing St. John's wort (Hypericum perforatum) should not be used while taking Mercilon due to the risk of decreased plasma concentrations and reduced clinical effects of Mercilon (see Section 4.5 Interactions).

**Reduced cycle control**

With all CHCs, 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 tablet-free interval. If the CHC has been taken according to the directions described in Section 4.2, it is unlikely that the woman is pregnant. However, if the CHC 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 CHC use is continued.

## 4.5 Interaction with other medicinal products and other forms of interaction

**Interactions**

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

**Effect of other medicinal products on Mercilon**

Interactions can occur with medicinal or herbal products that induce microsomal enzymes, **specifically cytochrome P450 enzymes (CYP),** which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Management
Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme-inducing medicinal or herbal products should temporarily use a barrier method or another method of contraception in addition to the Mercilon. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

Long-term treatment
In women on long-term therapy with enzyme-inducing active substances, another reliable, non-hormonal method of contraception unaffected by enzyme inducing medicinal products is recommended.

The following interactions have been reported in literature:
Substances increasing the clearance of Mercilon (enzyme induction) e.g.
Phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, some HIV protease inhibitors (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine), and possibly also oxcarbazepine, topiramate, rifabutin, felbamate, griseofulvin, and products containing the herbal remedy St. John's wort.

**Substances with variable effects on the clearance of Mercilon**

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 progestagens, including etonogestrel or estrogens. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

**Substances decreasing the clearance of Mercilon (enzyme inhibitors)**
The clinical relevance of potential interactions with enzyme inhibitors remains unknown.
Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of estrogens or progestagens, including etonogestrel.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

**Effects of Mercilon on other medicinal products**

Hormonal contraceptives COC's may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g., ciclosporine) or decrease (e.g. lamotrigine).

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration

*Pharmacodynamic interactions*
Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Mercilon users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Mercilon can be restarted 2 weeks following completion of treatment with this combination drug 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 metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

## 4.6 Fertility, Pregnancy and Lactation

Mercilon is not indicated during pregnancy. If pregnancy occurs during treatment with Mercilon, further intake should be stopped. However, most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used CHCs prior to pregnancy, nor a teratogenic effect when CHCs were taken inadvertently during pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting Mercilon (see sections 4.2 and 4.4).

Lactation may be influenced by CHCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of CHCs 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 Undesirable Effects

*Description of selected adverse reactions*
An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Other undesirable effects have been reported in women using CHCs: these are discussed in more detail in section 4.4.

As with all CHCs, changes in vaginal bleeding patterns may occur, especially during the first months of use. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration.

Possibly related undesirable effects that have been reported in users of Mercilon or CHC users in general are listed in the table below[1]: . All ADRs are listed by system organ class and frequency; common (≥1/100), uncommon (≥1/1000 to <1/100) and rare (<1/1000).

| System Organ Class | Common | Uncommon | Rare | Not Known |
|---|---|---|---|---|
| Immune system disorders | | | Hypersensitivity | Exacerbation of symptoms of hereditary and acquired angioedema |
| 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, diarrhoea | 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 common appropriate MedDRA term to describe a certain adverse event reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.
[2]Incidence in observational cohort studies of ≥1/10000 to <1/1000 women years

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 to ADR Reporting at www.medicinesauthority.gov.mt/adrportal .

## 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.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

ATC classification G03A A09.
The contraceptive effect of CHCs 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, CHCs have several positive properties which, next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. In the largest multicenter trial (n=26 822 cycles), the uncorrected Pearl Index is estimated at 0.18 (95% confidence interval 0.05 – 0.46). Furthermore, 7.2% of the women reported absence of withdrawal bleeding and 12.5% reported occurrence of irregular bleeding after 6 month treatment cycles.
Apart from this, with the higher-dosed CHCs (50µg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed CHCs remains to be confirmed.

Paediatric population

No clinical data on efficacy and safety are available in adolescents below 18 years.

## 5.2 Pharmacokinetic Properties

**Desogestrel**

*ABSORPTION*
Orally administered desogestrel is rapidly and completely absorbed and converted to etonogestrel. Peak serum concentrations are reached at about 1.5 hours. 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 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 extracted 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 completely absorbed. Peak serum concentrations are reached within 1-2 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 l/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 glucronides and sulphate. The metabolic clearance rate is about 5 ml/min/kg.
In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2.

*ELIMINATION*
Ethinylestradiol serum levels decrease in two disposition phases, the terminal disposition phase is characterised by a half-life of approximately 24 hours. Unchanged drug is not excreted; ethinylestradiol metabolites are excreted at 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% compared to single dose.

## 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans when CHCs are used as recommended. This is based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

All-rac-α-tocopherol
Potato starch
Povidone
Stearic acid
Silica,colloidal anhydrous
Lactose Monohydrate

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf-life

3 years

## 6.4 Special precautions for storage

Store below 25ºC. Store in the original package in order to protect from light.

## 6.5 Nature and contents of containers

PVC/aluminium blister, which is packed in an aluminium laminated sachet.
Pack sizes: 3 x 21 tablets.
Each blister contains 21 tablets.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
NL-5349 AB Oss
The Netherlands

# 8. MARKETING AUTHORISATION NUMBER

MA 031/02301

# 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 October 2005
Date of last renewal: 01 July 2010

# 10. DATE OF REVISION OF THE TEXT

June 2026