1. NAME OF THE MEDICINAL PRODUCT

Mercilon® tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.150 mg desogestrel and 0.020 mg ethinylestradiol.

Excipient: lactose < 80 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral use

Tablets are round, biconvex and 6 mm in diameter. They are coded on one side TR above 4 and on the reverse side Organon*.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral Contraception.

4.2 Posology and method of administration

4.2.1 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.

4.2.2 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 days 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 substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or 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.

If the woman has been using her previous method consistently and correctly and if it is reasonably certain that she is not pregnant she may also switch from her previous combined hormonal contraceptive on any day of the cycle.

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

Following first-trimester abortion
The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion

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 additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

The increased risk of VTE during the postpartum period should be considered when restarting Mercilon® (see section 4.4).

4.2.3 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 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 tablet-free interval, the higher the risk of a pregnancy.

- **Week 2**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- **Week 3**

The risk of reduced reliability is imminent because of the forthcoming 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 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 a woman misses tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.

4.2.4 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 in section 4.2.3, 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.

4.2.5 How to shift periods or how to delay a period

To delay a period 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 presence of any of the conditions listed below. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
  - 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 Warnings/Precautions).
  - A high risk of venous thromboembolism due to the presence of multiple risk factors (see Warnings/Precautions).

- 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 Warnings/Precautions) 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 values have not returned to normal; cholestatic jaundice; a history of jaundice of pregnancy or jaundice due to the use of steroids; Rotor syndrome and Dubin-Johnson syndrome.
- 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 active substances of Mercilon® or to any of the excipients.
- Endometrial hyperplasia.
- Porphyria.
- A history during pregnancy or previous use of steroids of severe pruritus or herpes gestationis.
- Mercilon® is contraindicated for use with the Hepatitis C virus combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section 4.4).

4.4 Special warnings and special precautions for use

4.4.1 Warnings

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

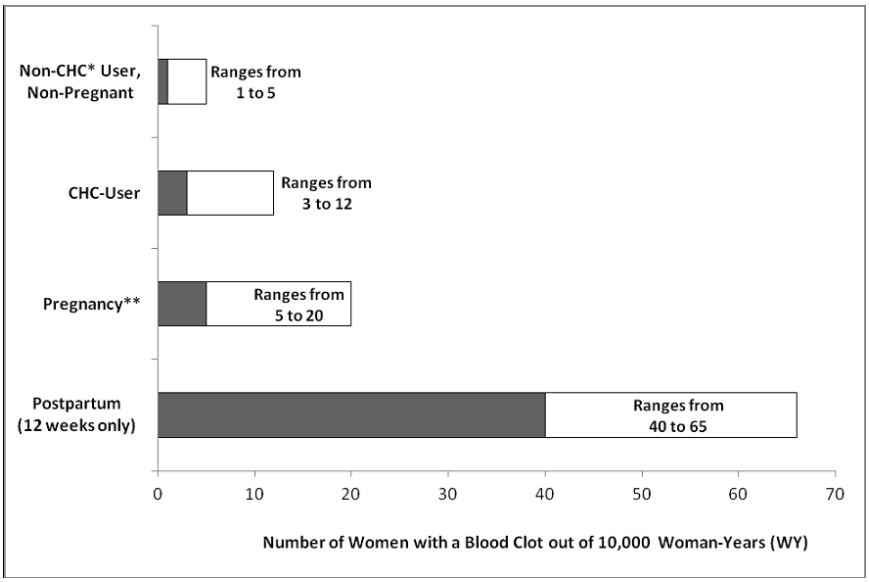
Throughout this section the general term combined hormonal contraceptive (CHC) is used when data exist for oral and non-oral contraceptives. The term combined oral contraceptive (COC) is used when data exist only for oral contraceptives.

1. Circulatory Disorders

- Epidemiological studies have shown an association between the use of CHCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.
- The use of any CHCs is associated with an increased risk of venous thromboembolism (VTE) manifesting as deep venous thrombosis and/or pulmonary embolism. The risk is highest during the first year a woman ever uses a CHC. The risk is also increased after initially starting a CHC or restarting the same or different CHC after a break in use of 4 weeks or more.
- Some epidemiological studies have suggested that women using low-dose COCs with third generation progestogens, including desogestrel, have an increased risk of VTE compared with those using low-dose COCs with the progestogen levonorgestrel. These studies indicate an approximate 2-fold increase in risk, which would correspond to an additional 1-2 cases of VTE per 10 000 women years of use. However, data from other studies have not shown this 2-fold increase in risk.
- Overall, the incidence of VTE in users of low estrogen dose (< 0.05 mg ethinylestradiol) CHCs ranges from about 3 to 12 cases per 10 000 women years compared to 1 to 5 cases per 10 000 women years

in non-CHC users. The incidence of VTE occurring during CHC use is less than the incidence associated with pregnancy (i.e., 5 to 20 cases per 10 000 women years). VTE is fatal in 1-2% of cases.

- It is estimated that out of 10 000 women who use a CHC containing desogestrel, between 9 to 12 women will develop a VTE in one year; this compares with about 6 in women who use a levonorgestrel-containing CHC.
- The figure below shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, for pregnant women, and for women in the postpartum period. To put risk of developing a VTE into perspective: If 10 000 women who are not pregnant and do not use CHCs are followed for one year, between 1 and 5 of these women will develop VTE.
- Likelihood of Developing a VTE.



*CHC=combined hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10 000 WY.

- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in CHC users.
- Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident 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 or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
  - obesity (body mass index over 30 kg/m^2);

- prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization. (See also section 4.3 'Contraindications');
- and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.

- The risk of arterial thromboembolic complications increases with:
  - increasing age;
  - smoking (with 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 thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.

- The increased risk of thromboembolism in the puerperium must be considered (for information on "Pregnancy and Lactation" see section 4.6).
- Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
- An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.
- Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis.

2. Tumours

- The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Epidemiological studies have indicated that long-term use of COCs contributes to this increased risk but there continues to be uncertainty about the extent to which this finding is attributable to confounding effects, like increased cervical screening and difference in sexual behavior including use of barrier contraceptives, or a causal association.

- 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.

3. Hepatitis C

- During clinical trials with some HCV combination drug regimens, ALT elevations were observed in women using ethinylestradiol containing medications (see section 4.5.1). For example, 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. Mercilon® must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see sections 4.3 and 4.5). Mercilon® 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.
- Exogenous estrogens may induce or exacerbate symptoms or hereditary and acquired angioedema.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. 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.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.
- Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg 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.
- During the use of estrogen-containing oral contraceptives, depression may occasionally occur. If this is accompanied by a disturbance in tryptophan metabolism, administration of vitamin B6 might be of therapeutic value.
- Patients with any of the following conditions should be monitored:

  1. latent or overt cardiac failure, renal dysfunction, hypertension, epilepsy or migraine (or a history of these conditions), since aggravation or recurrence may occasionally be induced.

  2. sickle cell haemoglobinopathy, since under certain circumstance, e.g., during infections or anoxia, estrogen-containing preparations may induce thromboembolic processes in patients with this condition.

  3. estrogen-sensitive gynaecological disorders, e.g., uterine fibromyomata which may increase in size, and endometriosis which may become aggravated during estrogen treatment.
- Mercilon® 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 counseling the choice of contraceptive method(s), all the above information should be taken into account.

4.4.2 Medical Examination/Consultation

Prior to the initiation or reinstitution of Mercilon® a complete medical history (including family history) should be taken 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 (section 4.3) and warnings (section 4.4). The woman should also be instructed to carefully read the user 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 the individual woman.

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

4.4.3 Reduced efficacy

The efficacy of Mercilon® may be reduced in the event of e.g., missed tablets (section 4.2.3), gastro-intestinal disturbances (section 4.2.4) or concomitant medications that decrease the plasma concentration of etonogestrel, the active metabolite of desogestrel (section 4.5.1).

4.4.4 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 tablet-free interval. If the COC has been taken according to the directions described in section 4.2, 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.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 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 Mercilon®. These products include phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, rifabutin, and possibly also oxcarbazepine, 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 (Hypericum Perforatum).

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 Mercilon® may be reduced. A barrier contraceptive method should be used in addition to Mercilon® 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 tablets in the current COC pack, the next COC pack should be started right away without the usual tablet-free 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) CYP3A4 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. Mercilon® must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see sections 4.3 and 4.4). Mercilon® can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

Concomitant use with some other HCV antiviral medicinal products, such as those containing glecaprevir/pibrentasvir, may increase the risk of ALT elevations (see section 4.4.1).

4.5.2 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 Pregnancy and lactation

Mercilon® is not indicated during pregnancy. If pregnancy occurs during treatment with Mercilon®, 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.

The increased risk of VTE during the postpartum period should be considered when re-starting Mercilon® (see Warnings/Precautions).

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 Undesirable effects

Possibly related undesirable effects that have been reported in clinical trials or observational studies with Mercilon® or CHC users in general are listed in the table below[1]:

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
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 MedDRA 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 in observational cohort studies of ≥ 1/10000 to < 1/1000 women-years.

A number of undesirable effects have been reported in women using combined oral contraceptives, which are discussed in more detail in section 4.4 Special Warnings and Precautions for Use. These include: venous thromboembolic disorders; arterial thromboembolic disorders; hypertension; hormone-dependent tumours (e.g., liver tumours, breast cancer); exacerbations of hereditary and acquired angioedema; chloasma; cholelithiasis (gallstone formation), cholestatic jaundice.

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 COCs 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. Besides protection against pregnancy, COCs 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. Apart from this, with the higher-dosed COCs (50 µ g ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs remains to be confirmed.

5.2 Pharmacokinetic properties

5.2.1 Desogestrel

ABSORPTION

Orally administered desogestrel is rapidly and completely 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 - 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 metabolized 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 characterized 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.

5.2.2 Ethinylestradiol

ABSORPTION

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

about 45 pg/ml 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 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.

ELIMINATION

Ethinylestradiol serum levels decrease in two disposition 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

Preclinical data reveal no special hazard for humans when COCs 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

silica colloidal anhydrous
lactose monohydrate
potato starch
povidone
stearic acid
all-*rac-alpha*-tocopherol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the tablets is as indicated on the box, if stored according to the directions in section 6.4.

6.4 Special precautions for storage

Store at or below 30°C. Do not freeze.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/aluminium blister, which is packed in an aluminium laminated sachet.

Pack sizes: 21, 3 x 21 and 6 x 21 tablets.

Each blister contains 21 tablets.

Not all presentations may be available locally.

Product Registrant

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ORGANON