

1. NAME OF THE MEDICINAL PRODUCT

Mercilon®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.150 mg desogestrel and 0.020 mg ethinylestradiol.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 interval or following the last placebo tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Mercilon

preferably on the day of removal, but at the latest when the next application would have been due.

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.

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

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

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see under 'Special Warnings and Special Precautions for Use').

- 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.
- Presence or history of liver tumors (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.

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

1. Circulatory Disorders

- Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.
- The use of any COC 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 COC.
- 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) OCs is considered to be up to 4 per 10 000 women years compared to 0.5-3 per 10 000 women years in non-OC users. The incidence of VTE occurring during COC use is less than the incidence associated with pregnancy (i.e. 6 per 10 000 pregnant women years).
- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.
- 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 or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:
 - age;
 - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
 - a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
 - obesity (body mass index over 30 kg/m²);
 - dyslipoproteinaemia;
 - hypertension;
 - migraine
 - valvular heart disease;
 - atrial fibrillation;
 - prolonged 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.

- There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.
- The increased risk of thromboembolism in the puerperium must be considered (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 and that the risk associated with pregnancy is higher than that associated with low-dose COCs (< 0.05 mg ethinylestradiol).

2. *Tumors*

- The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behavior including use of barrier contraceptives.
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age,

the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

- In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.
3. *Other conditions*
- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
 - Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
 - The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
 - 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.

4.4.2 Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of COC use, guided by the contraindications (Section 4.3) and warnings (Section 4.4.1), and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g., a transient ischaemic attack, etc.) or risk factors (e.g., a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

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

4.4.3 Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g., missed tablets (Section 4.2.3), gastro-intestinal disturbances (Section 4.2.4) or concomitant medication (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

Interactions between oral contraceptives and other drugs 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 drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g., phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, ritonavir, griseofulvin and products containing St. John's wort).

Interference with Enterohepatic Circulation: Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g., penicillins, tetracyclines).

Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

Oral contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g., cyclosporin).

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

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.

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 observed effects.

4.8 Undesirable effects

The most serious undesirable effects associated with the use of COCs are listed in Section 4.4.1.

Other side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are:¹

Body system	Common/Uncommon (more than 1/1000)	Rare (less than 1/1000)
Eye disorders		Contact lens intolerance
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhea	
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders	Weight increased, fluid retention	Weight decreased
Nervous system disorders	Headache, migraine, libido decreased, depressed mood, mood altered	Libido increased
Reproductive system and breast disorders	Breast pain, breast tenderness, breast hypertrophy	Vaginal discharge, breast discharge
Skin and subcutaneous tissue disorders	Rash, urticaria	Erythema nodosum, erythema multiforme

¹ The most appropriate MedDRA term (version 6.1) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

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

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, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dosed (0.050 mg ethinylestradiol) COCs have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

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 is 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 risk for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

The daily amount of lactose (< 80 mg) is such that women with an intolerance to lactose are highly unlikely to experience a problem.

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 2°C to 30°C, protected from light and moisture.

6.5 Nature and contents of container

Push-through strips of 21 white tablets each. Tablets are round, biconvex and 6 mm in diameter. They are coded on one side TR above 4 and on the reverse side Organon*.

The push-through strip is a polyvinylchloride (PVC)/aluminum blister consisting of PVC film backed by aluminum foil with a heat-seal coating. Each blister is packed in a sealed aluminum laminated sachet. The sachets are packed in a printed cardboard box together with the package leaflet (1, 3 or 6 sachets per box).

6.6 Instructions for use and handling <and disposal>

Store all drugs properly and keep them out of reach of children.

7. MARKETING AUTHORISATION HOLDER

[Market specific information must be included in this section where applicable]

8. MARKETING AUTHORISATION NUMBER(S)

[Market specific information must be included in this section where applicable]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Market specific information must be included in this section where applicable]

10. DATE OF REVISION OF THE TEXT

September 2004