1. NAME OF THE MEDICINAL PRODUCT

MERCILON®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

desogestrel (a progestagen)	0.15 mg
ethinylestradiol (an estrogen)	0.02 mg

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral 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

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 Mercilon

No preceding hormonal contraceptive use [in the past month]:

It is preferable that tablet intake from the first pack is started on the first day of menstruation in which case no extra contraceptive precautions are necessary.

If menstruation has already begun, (that is 2, 3, or 4 days previously), tablet taking should commence on day 5 of the menstrual period. In this case additional contraceptive precautions must be taken for the first 7 days of tablet taking.

If menstruation began more than 5 days previously then the patient should be advised to wait until her next menstrual period before starting to take Mercilon.

Changing from a 21 day pill or another 22 day pill to Mercilon:

All tablets in the old pack should be finished. The first Mercilon tablet is taken the next day i.e. no gap is left between taking tablets nor does the patient need to wait for her period to begin. Tablets should be taken as instructed in 'How to take Mercilon'. Additional contraceptive precautions are not required. The patient will not have a period until the end of the first Mercilon pack, but this is not harmful, nor does it matter if she experiences some bleeding on tablet-taking days.

Changing from a combined Every Day Pill (28 day tablets) to Mercilon:

Mercilon should be started after taking the last *active* tablet from the 'Every Day Pill' pack (i.e. after taking 21 or 22 tablets). The first Mercilon tablet is taken the next day i.e. no gap is left between taking tablets nor does the patient need to wait for her period to begin. One tablet is taken daily at the same time, without interruption for 21 days, followed by a 7 day tablet-free period. Each subsequent pack is started after the 7 day tablet-free period has elapsed. Additional contraceptive precautions are not required. Remaining tablets from the Every Day (ED) pack should be discarded. The patient will not have a period until the end of the first Mercilon pack, but this is not harmful, nor does it matter if she experiences some bleeding on tablet-taking days.

Changing from a Progestogen-only Pill (POP or Mini Pill) to Mercilon:

The first Mercilon tablet should be taken on the first day of the period, even if the patient has already taken a mini pill on that day. One tablet is taken daily at the same time, without interruption for 21 days, followed by a 7 day tablet-free period. Each subsequent pack is started after the 7 day tablet-free period has elapsed. Additional contraceptive precautions are not then required. All the remaining Progestogen-only pills in the mini pill pack should be discarded.

If the patient is taking a (mini) pill, then she may not always have a period, especially when she is breast feeding. The first Mercilon tablet should be taken on the day after stopping the mini pill. All remaining pills in the mini pill packet must be discarded. Additional contraceptive precautions must be taken for the first seven days.

Changing from a progestogen-only injection, implant or from a progestogen- releasing intrauterine system [IUS]:

The woman may switch any day from an implant (or the IUS on the day of its removal, from an injectable when the next injection would be due). Additional contraceptive precautions must be taken for the first seven days.

Post-Partum Administration:

Following childbirth hormonal contraceptive administration to non-breast feeding mothers should be started 21 days post-partum in which case no additional contraceptive precautions are required. If intercourse has taken place post-partum, hormonal contraceptive use should be delayed until the first day of the menstrual period.

If post-partum administration of Mercilon begins more than 21 days after delivery then additional contraceptive precautions are required for the first 7 days.

N.B. (Nota Bene): Mothers who are breast feeding should be advised not to use the combined pill since this may reduce the amount of breast-milk, but may be advised instead to use a progestogen-only pill (POP).

After miscarriage or abortion administration should start immediately in which case no additional contraceptive precautions are required.

Additional contraceptive precautions:

When additional contraceptive precautions are required the patient should be advised either not to have sex, or to use a cap plus spermicide, or for her partner to use a condom.

Rhythm methods should not be advised as the pill disrupts the usual cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

How to skip a period:

To skip a period, a new pack of Mercilon should be started on the day after finishing the current pack (the patient skips the tablet-free days). Tablet-taking should be continued in the usual way. During the use of the second pack she may experience slight spotting or breakthrough bleeding but contraceptive protection will not be diminished provided there are no tablet omissions. The next pack of Mercilon is started after the usual 7 tablet-free days, regardless of whether the period has completely finished or not.

4.2.3 Management of missed tablets

Advice in case of missed pills

The reliability of Mercilon may be reduced if tablets are forgotten:
If the forgotten tablet is taken within 12 hours, no further precautions are necessary, further tablets should be taken at the usual time.

If one or more tablets are forgotten for more than 12 hours, contraceptive protection will be reduced.
The patient should take the last forgotten tablet, even if this means taking two tablets in one day, and then continue to take tablets at the normal time. Additional contraceptive precautions should be taken for the next seven days, and the patient should follow 'the 7-day rule'.

The 7-Day rule

If any one tablet is forgotten for more than 12 hours
If the patient has vomiting or diarrhoea for more than 12 hours
If the patient is taking any of the drugs listed under 'Interactions':
The patient should continue to take her tablets as usual and additional contraceptive precautions must be taken for the next 7 days.

But - if these 7 days run beyond the end of the current pack, the next pack must be started as soon as the current one is finished, i.e. no gap should be left between packs. (This prevents an extended break in tablet taking which may increase the risk of the ovaries releasing an egg and thus reducing contraceptive protection). The patient will not have a period until the end of 2 packs but this is not harmful nor does it matter if she experiences some bleeding on tablet taking days.

Advice in case of Vomiting or severe diarrhoea

In case of severe gastro-intestinal disturbance, absorption may not be complete and additional contraceptive measures should be taken. Unless diarrhoea is extremely severe, it does not affect steroidal absorption.

If vomiting occurs within 3-4 hours after tablet taking, or in cases of severe or prolonged diarrhoea, 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.

4.2.4 Paediatric population

The safety and efficacy of desogestrel in adolescents below 18 years has not yet been established. No data are available.

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 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 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 tumours (benign or malignant).
- Known or suspected estrogen-dependent tumours, (See 4.4 Special warnings and special precautions for use: Tumours).
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- 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 or medicinal products containing glecaprevir/pibrentasvir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

4.4.1 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.

1. Circulatory Disorders

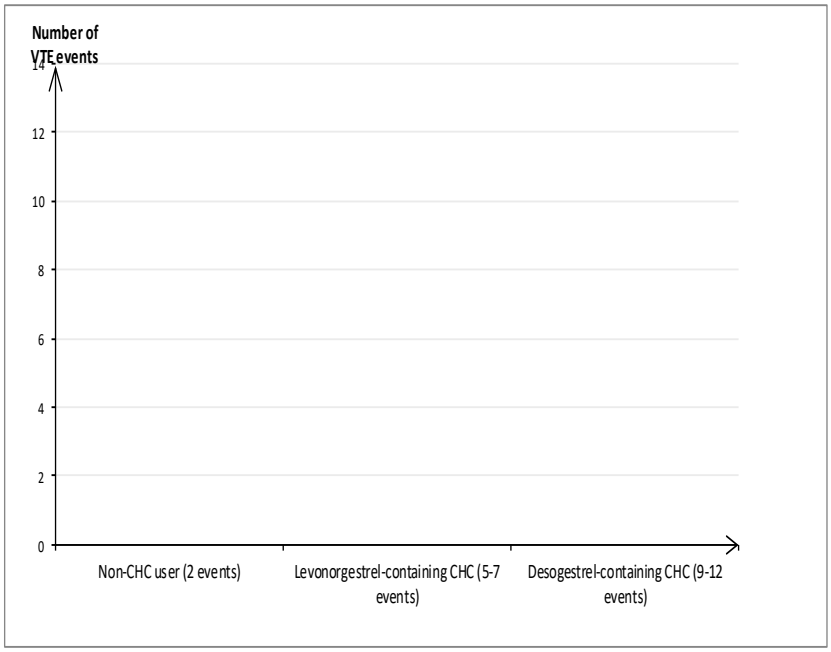
Risk of venous thromboembolism (VTE)

- 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 of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

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. 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 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. 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. before 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. Particularly important in women with additional risk factors.
Positive family history (arterial thromboembolism ever in a sibling or parent especially at 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

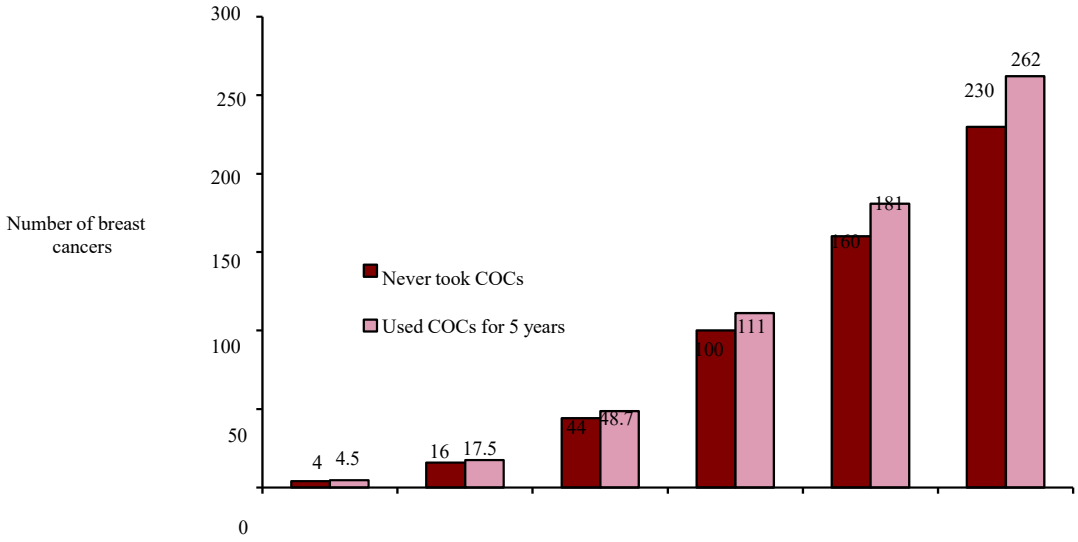
- An increased risk of cervical cancer in long term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs). 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 additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.
- Breast cancer is rare among women under 40 years of age whether or not they take COCs. Whilst this background risk increases with 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 (see bar chart).

- The most important risk factor for breast cancer in COC users is the age women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess.

- The possible increase in risk of breast cancer should be discussed with the user and weighed against the benefits of COCs taking into account the evidence that they offer substantial protection against the risk of developing certain other cancers (e.g. ovarian and endometrial cancer).

Estimated cumulative numbers of breast cancers per 10,000 women diagnosed in 5 years of use and up to 10 years after stopping COCs, compared with numbers of breast cancers diagnosed in 10,000 women who had never used COCs



Took the Pill at these ages:	Under 20	20-24	25-29	30-34	35-39	40-44
Cancers found up to the age of:	30	35	40	45	50	55

- 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 haemorrhages. A hepatic tumour should be considered in the differential diagnosis when upper abdominal pain, enlarged liver 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). Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see sections 4.3 and 4.5).

4. Other conditions

- Women with hypertriglyceridemia, 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 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 CHC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred previously during pregnancy or 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 ulcerative colitis have been associated with 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 this preparation.
- Mercilon contains < 80 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take medicine.

Relative Contraindications

Severe depression or a history of this condition. 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.

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 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. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method.

4.4.3 Reduced Efficacy

The efficacy of Mercilon may be reduced in the event of missed tablets (Section 4.2.3), gastrointestinal 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/ irregular bleeding

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

4.5.1 Interactions

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or 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, modafinil, topiramate, felbamate, griseofulvin, some HIV protease inhibitors (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz) and products containing the herbal remedy St. John’s wort.

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

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.

- 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.

- 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 interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be increased (e.g., ciclosporin) or decreased (e.g., lamotrigine).

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

Pharmacodynamic interactions

Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, or glecaprevir / pibrentasvir 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.

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 for use 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 early 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

As with all COCs, 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.

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.

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 (≥1/1,000 to < 1/100), rare (<1/1,000) and not known (cannot be estimated from the available data).

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	Vomiting, diarrhoea		
Skin and subcutaneous tissue disorders		Rash, urticaria	Erythema nodosum, erythema multiforme	
Reproductive	Breast pain,	Breast	Vaginal discharge,	

system and breast disorders	breast tenderness	enlargement	breast discharge	
Investigations	Weight increased		Weight decreased	

[1] The most appropriate MedDRA term (version 11) 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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://sideeffects.health.gov.il)

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 slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens and estrogens, fixed combinations, ATC code: G03AA09

Mercilon is an oral contraceptive combination containing 150 micrograms desogestrel and 20 micrograms ethinylestradiol.

Ethinylestradiol is a well-known synthetic estrogen.

Desogestrel is a synthetic progestogen. After oral administration it has a strong ovulation-inhibiting activity, a strong progestational and anti-estrogenic activity, no estrogenic activity, very weak androgenic/anabolic activity.

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.

Biotransformation

Etonogestrel is completely metabolized by the known pathways of steroid metabolism, including cytochrome P450 3A4. 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 a 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 presystemic conjugation and first-pass metabolism is approximately 60%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 l/kg was determined.

Biotransformation

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 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 studies on ethinylestradiol and desogestrel revealed no special hazard for humans 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

Lactose monohydrate
Potato starch
Povidone
Stearic acid
Silica, colloidal anhydrous
All-rac-1-α-Tocopherol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store 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

Push-through blisters with 21 white tablets.

The push-through pack is a PVC/Al blister consisting of aluminium foil with a heat-seal coating and a PVC film. Each blister, which contains 21 tablets, is packed in a printed aluminium/polyethylene/polyester pouch. The pouch is packed in a printed cardboard box together with the package leaflet (1 or 3 sachets per box). Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

See section 4.2.

6.7 Marketing Authorization number

103.11.26498

Manufacturer: Organon LLC, NJ USA

License holder and address:
Organon Pharma Israel Ltd., 1 Atir Yeda, Kfar Saba

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