

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mylite 100 micrograms / 20 micrograms coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 100 micrograms of levonorgestrel and 20 micrograms of ethinylestradiol.

Excipients with known effect:

Each coated tablet contains 48.23 mg of lactose monohydrate and 14.38 mg of sucrose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

Pink, round (5.60 mm diameter), coated, biconvex tablets, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral contraception.

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

4.2 Posology and method of administration

Posology

How to take Mylite

Tablets must be taken orally in the order directed on the blister package at about the same time every day, with some liquid if necessary. 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.

The bleeding usually starts within 2 to 3 days after the last tablet and may not end before the next pack is started.

How to start taking of Mylite

- No preceding hormonal contraceptive use (in the past month)

Tablet-taking is started 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 in that case an additional barrier method is recommended for the first 7 days of the first cycle.

- Changing from another combined hormonal contraceptive (combined oral contraceptive(COC), vaginal ring, transdermal patch)

The women should start with levonorgestrel/ethinylestradiol preferably on the day after the last hormone containing tablet of the previous COC, but at the latest on the day following the usual tablet-free break or the last hormone-free tablet of the previous hormonal contraceptive. In case of a vaginal ring or transdermal patch has been used, the woman should start levonorgestrel/ethinylestradiol preferably on the day of removal, but at the latest when the next application would have been due.

- Changing from a progestogen-only method (oral pill, injection, implant) or intrauterine system (IUS)

The woman can switch to Mylite 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 use an additional barrier method for the first 7 days of tablet-taking.

- Following first-trimester abortion

The use of the tablets can start immediately. In such a case, no other contraceptive measures are needed.

- Following delivery or second-trimester abortion

For breast-feeding, see section 4.6 Fertility, Pregnancy and Lactation.

The use of the tablets is started 21 to 28 days after delivery or second-trimester abortion. When starting later, an additional barrier method must be used for the first 7 days of tablet-taking. If the woman has already had sexual intercourse, pregnancy must be excluded before the actual start of COC use or the woman has to wait for her next menstrual period.

Management of missed tablets

The following recommendations are applicable in case of missing active tablets:

Mylite contains a very low dose of both hormones, and, as a consequence, the contraceptive efficacy margin is small, if a pill is missed. If the woman 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 take the next tablets at the usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced.

The following two basic rules apply in cases where tablets have been missed:

1. Tablet-taking must never be discontinued for longer than 7 days.
2. Adequate suppression of the hypothalamic-pituitary-ovarian axis requires 7 days of uninterrupted tablet-taking.

Accordingly, the following advice can be given for daily practice:

Week 1

The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take the next tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If the woman has had sexual intercourse in the 7 days before missing the tablet, the possibility of a pregnancy must be considered. The more tablets have been missed and the closer they are to the regular tablet-free break, the higher the risk of pregnancy.

Week 2

The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take the next 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. If she has not taken the tablets correctly or has missed more than one tablet, she should be advised to use extra contraceptive precautions for the next 7 days.

Week 3

The risk of reduced contraceptive reliability is imminent because of the forthcoming tablet-free break of 7 days. However, reduced contraceptive protection can still be prevented by adjusting the dosage. By adhering to the following advice, there is no need to use extra contraceptive precautions, provided that all the tablets have been taken correctly in the 7 days preceding the first missed tablet. If this is not the case, the woman should follow the first of these two options and use extra contraceptive precautions for the next 7 days as well.

1. The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take the next tablets at her usual time. The next pack is started as soon as the current pack is finished, i.e. there is no tablet-free break. There will probably be no withdrawal bleed until the end of the second pack, but the woman may experience spotting or breakthrough bleeding on tablet-taking days.
2. It is also possible to stop taking tablets from the current pack. The woman must then have a tablet-free break of 7 days, including the days she missed tablets, and then continue with the next pack.

If the woman misses several tablets and has no withdrawal bleed during the first normal tablet-free break, the possibility of a pregnancy must be considered.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal symptoms, absorption of the active ingredients may not be complete and additional contraceptive measures should be taken.

If vomiting or severe diarrhea occurs within 3 to 4 hours after taking a tablet, the woman should apply the advice given for missed tablets. If the woman does not want to change her normal tablet schedule, she has to take the extra tablets from another pack.

How to change the starting day of a period or to delay a period

To delay a period the woman should start a new pack immediately after finishing the current pack without any break. Periods can be delayed as long as wished, but no later than till the end of the second pack. During this time the woman may experience breakthrough bleeding or spotting. Regular intake of Mylite is then resumed after the usual 7-day tablet-free break.

If the woman wants to change the starting day or her periods to another day of the week, she can be advised to shorten her next tablet-free break by as many days as she likes. The shorter the break, the higher the risk that there will be no withdrawal bleed and that the woman will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

Additional information on special populations*Pediatric population:*

Mylite is only indicated after menarche.

Elderly:

Not applicable. Mylite is not indicated after menopause.

Hepatic impairment

Mylite is contraindicated in women with severe hepatic diseases. See also section 4.3.

Renal impairment

Mylite has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Method of administration

Oral use.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the presence of any of the following conditions. Should any of the conditions appear for the first time during CHC use, the product must 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

- Severe hepatic disease, current or previous, as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Amenorrhoea of unknown cause
- Hypersensitivity to the active substances levonorgestrel, ethinylestradiol or to any of the excipients listed in section 6.1.

Mylite is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.4 and section 4.5).

4.4 Special warnings and precautions for use

Warnings:

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

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should be advised to contact her physician. The physician should then decide on whether COC use should be discontinued.

- 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. **The decision to use Mylite should be taken after a discussion with the woman to ensure she understands the risk of VTE with Mylite, 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.**

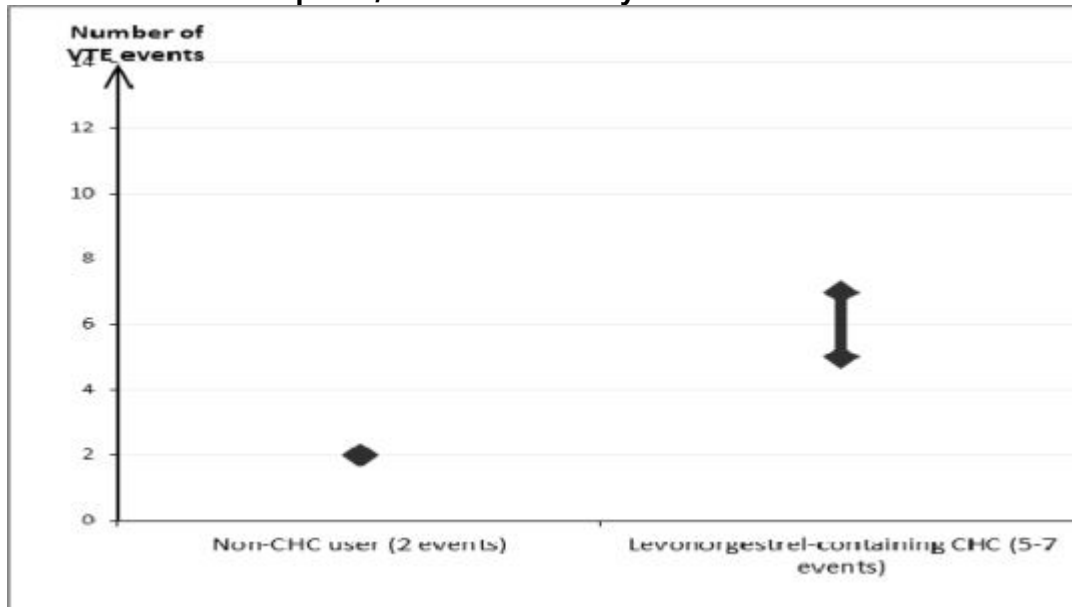
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated that out of 10,000 women who use a CHC that contains levonorgestrel, about 6¹ will develop a VTE in a year.

This number of VTEs per year is fewer than the number expected in women during pregnancy or in the postpartum period.

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

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



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).

¹ 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

Mylite 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/m ²)	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 pill (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 Mylite 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 "Fertility, 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). Mylite 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	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before

early age e.g. below 50)	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.

Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

- *Tumours*

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

A meta-analysis of 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. This excess risk gradually disappears during the course of 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide

evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

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

- *Other conditions*

Women with hypertriglyceridemia, 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. Only in these rare cases an immediate discontinuation of COC use is justified. A systematic relationship between COC use and clinical hypertension has not been established. If, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. 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 during both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis, gallstones, porphyria, systemic lupus erythematosus, haemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss depressive mood.

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

Acute or chronic disturbances of liver function may necessitate discontinuation of COC use until the liver function values return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or previous use of sex steroids necessitates 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 (<0.05 mg ethinylestradiol). However, diabetic women should be carefully monitored, particularly in the early stage of COC use.

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the 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 frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

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. Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during 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.

Medical examination/consultation

Prior to the initiation or reinstatement of levonorgestrel/ethinylestradiol 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 contra-indications (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 levonorgestrel/ethinylestradiol 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 transmissible diseases.

Reduced efficacy

The efficacy of COCs may be reduced, in the event of missed tablets vomiting or diarrhoea or concomitant medication.

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 period of about three cycles. In users of Mylite, any bleeding (spotting and/or break-through bleeding) was reported by more than 50% during the first 6 months of use.

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.

Excipients

The tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The tablet contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

- Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.
- Effects of other medicinal products on Mylite

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, may increase the risk of ALT elevations (see sections 4.3 and 4.4).

Therefore, Mylite-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these drug regimens. Mylite can be restarted 2 weeks following completion of treatment with these drug regimens.

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Management

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

Short-term treatment

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

If the drug therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.

Long-term treatment

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

Reduced absorption: Drugs that increase gastrointestinal motility, e.g. metoclopramide, may reduce hormone absorption.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction). *e.g.*: Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (*hypericum perforatum*).

Substances with variable effects on the clearance of COCs, e.g.

When co-administered with COCs, many HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV protease inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

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

Substances decreasing the clearance of COCs (enzyme inhibitors)

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen or the progestin or both.

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

- Effects of COCs on other medicinal products

COCs may interfere with the metabolism of other drugs. Increased plasma concentrations of cyclosporin have been reported with concomitant administration of COCs. COCs have been shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of lamotrigine.

Troleandomycin may increase the risk of intrahepatic cholestasis during co-administration with COCs.

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

Other forms of interactions

- 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 blood coagulation and fibrinolysis. The changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy

Mylite tablet is not indicated during pregnancy.

If the woman becomes pregnant while using Mylite, further intake must be stopped immediately.

However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women taking contraceptive pills prior to pregnancy, nor any teratogenic effects at unintentional intake of contraceptive pills in early pregnancy.

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

Breastfeeding

Lactation may be influenced by contraceptive pills since they may reduce the amount of breast milk and change its composition. Thus, the use of combined oral contraceptives should generally not be recommended until the nursing mother has weaned her child off breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the infant.

4.7 Effects on ability to drive and use machines

Mylite tablet has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions with Mylite are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in $\geq 1\%$ to $<10\%$ of users.

Serious adverse reactions are arterial and venous thromboembolism.

Tabulated list of adverse reactions

Adverse drug reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); and rare ($\geq 1/10,000$ to $<1/1,000$).

Adverse effects that have been reported in users of combined hormonal contraceptives including Mylite are*:

Organ system	Common ($\geq 1/100$ to $<1/10$)	Uncommon ($\geq 1/1000$ to $<1/100$)	Rare ($< 1/10,000$ to $<1/1000$),
Eye disorders			contact lens intolerance
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhoea	
Immune system disorders			hypersensitivity
Investigations	weight increased		weight decreased
Metabolism and nutrition disorders		fluid retention	
Nervous system disorders	headache	migraine	
Psychiatric disorders	depressed mood, mood altered	libido decreased	libido increased
Reproductive system and breast disorders	breast tenderness, breast pain	breast enlargement	breast discharge, vaginal discharge
Skin and subcutaneous tissue disorders		rash, urticaria	erythema nodosum, erythema multiforme
Vascular disorders			Arterial thromboembolism (ATE), Venous thromboembolism (VTE)

* The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections 4.3 and 4.4):

Tumours

- The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.
- Liver tumours (benign and malignant)

Other conditions

- Increased risk of pancreatitis in women with hypertriglyceridemia
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis.
- Chloasma

Interactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

There have been no reports of serious adverse effects from overdose. Symptoms that may be caused by overdose are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and the treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations, ATC Code: G03AA07

The contraceptive effect of COCs is based on the interaction of various factors. The most important of these factors are the inhibition of ovulation and changes in the cervical mucus.

Clinical trials have been performed in 2498 women aged 18 to 40 years. The overall Pearl Index calculated from these trials was 0.69 (95% confidence interval 0.30 – 1.36) based on 15,026 treatment cycles.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption

Orally administered levonorgestrel is absorbed rapidly and completely. Peak serum concentrations of about 2.3 ng/ml are reached about 1.3 hours after taking a Mylite tablet. The bioavailability is nearly 100%.

Distribution

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only 1.1% of the total serum drug concentrations are present as free steroid, approximately 65% are specifically bound to SHBG and approximately 35% are non-specifically bound to albumin. The ethinylestradiol-induced increase in the SHBG concentration influences the relative distribution of levonorgestrel into different protein fractions. Induction of the binding protein causes an increase in the SHBG-bound fraction and a decrease in the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 l after a single dose.

Biotransformation

Levonorgestrel (LNG) is extensively metabolized. The most important metabolic pathways are the reduction of the $\Delta 4$ -3-oxo group and hydroxylations at positions 2 α , 1 β and 16 β , followed by conjugation. Furthermore, CYP3A4 is involved in the oxidative metabolism of LNG, however, *in vitro* data suggest that this metabolic route is less relevant than reduction and conjugation. The metabolic clearance rate from serum is approximately 1.0 ml/min/kg.

Elimination

Levonorgestrel levels in serum decrease in two phases. The terminal phase is characterized by a half-life of approximately 25 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary (feces) ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

Steady state

During the continuous use of Mylite, serum levonorgestrel levels increase about threefold reaching steady-state conditions during the second half of the treatment cycle. Levonorgestrel pharmacokinetics are influenced by the SHBG levels in serum, which are increased 1.5–1.6-fold during the use of estradiol. Therefore, the clearance rate from serum and the volume of distribution are slightly reduced at steady state (0.7 ml/min/kg and about 100 l).

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 50 pg/ml are reached within 1–2 hours after taking a Mylite tablet. During absorption and first-pass hepatic metabolism ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% (interindividual variation about 20–65%).

Distribution

Ethinylestradiol is highly (approximately 98%) but non-specifically bound to serum albumin, and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of ethinylestradiol is 2.8–8.6 l/kg.

Biotransformation

Ethinylestradiol is subject to significant gut and hepatic first-pass metabolism. Ethinylestradiol and its oxidative metabolites are primarily conjugated with glucuronide or sulfate. The metabolic clearance rate was reported to be about 2.3–7 ml/min/kg.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2.

Elimination

Ethinylestradiol levels in serum decrease in two phases characterized by half-lives of about 1 hour and 10–20 hours, respectively.

Ethinylestradiol is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of 4:6, and the half-life is about 1 day.

Steady state

Ethinylestradiol concentration in serum increases about twofold after continuous use of levonorgestrel/ethinylestradiol. Due to the variable half-life of the terminal phase in serum clearance and the daily administration, steady-state conditions are reached within about a week.

5.3 Preclinical safety data

Preclinical studies (general toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction) have not revealed other effects than those which can be explained based on the known hormone profile of ethinyl estradiol and levonorgestrel.

However, it should 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

Tablet core:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Povidone
Magnesium stearate

Coating:

Povidone
Talc
Glycerol
Isopropyl alcohol
Sucrose
Calcium carbonate
Macrogol 6000
Titanium dioxide (E171)
Iron oxide (red) (E172)
Iron oxide (yellow) (E172)
Carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions

6.5 Nature and contents of container

Tablets are packed in PVC/PVDC/Aluminium blisters

Pack sizes:

21 coated tablets (1 x 21)
63 coated tablets (3 x 21)
126 coated tablets (6 x 21)
273 coated tablets (13 x 21)

Each blister is packed in trilaminated pouch.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd., T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/183/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th February 2012

Date of last renewal: 28th October 2016

10 DATE OF REVISION OF THE TEXT

November 2020