

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Leonore 100 micrograms/20 micrograms Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One coated tablet contains 100 micrograms levonorgestrel and 20 micrograms ethinylestradiol.

Excipient(s) with known effect:

One coated tablet contains 30.17 mg lactose (as monohydrate) and 19.66 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

White, round, biconvex, coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral contraception.

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

4.2 Posology and method of administration

Posology

The tablets must be taken each day at about the same time, if necessary with some liquid, in the order indicated on the blister pack. One tablet must be taken daily for 21 consecutive days. Taking the tablets from the next blister pack begins after a 7-day break in which a withdrawal bleeding usually occurs. This generally begins 2-3 days after taking the last tablet and may still be ongoing when use of the next blister pack is started.

Starting to take Leonore

No previous intake of hormonal contraceptives in the last month

The first tablet should be taken on the first day of the cycle (on the first day of the menstrual period). If administration is started between day 2 and 5, a non-hormonal method should be used during the first 7 days of tablet intake.

Change from another combined hormonal contraceptive (combined oral contraceptive, vaginal ring, transdermal patch)

The use of Leonore is started on the day following the usual tablet-free (ring-free, patch-free) break or the last placebo tablet of the previous hormonal contraceptive.

Change from a progestogen mono-preparation (mini pill, injection preparation, implant) or from an intrauterine system (IUS)

In cases of previous use of the mini pill, the change may be made on any day. The change from an implant or intrauterine system must take place on the day of removal, and from an injection preparation at the time when the next injection would have been due. However, during the first 7 days of administration of Leonore, an additional non-

hormonal contraceptive measure (barrier method) is required.

After abortion in the first trimester

Leonore may be started immediately. In this case, no additional contraceptive measures are necessary.

After parturition or abortion in the second trimester

For breast-feeding, see section 4.6.

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.

Procedure in the event of a forgotten tablet

Leonore 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 the time for taking the tablet has been exceeded by **more than 12 hours**, the contraceptive protection will not be completely ensured. The probability of pregnancy is the higher, the nearer in time the forgotten tablet is to the intake-free interval.

In the event of forgotten tablets, the following two principles apply:

1. Tablet use must not be interrupted for longer than 7 days.
2. Use of the tablets for at least 7 days is necessary to achieve adequate suppression of the hypothalamic-pituitary-ovarian system.

Accordingly, the following procedure applies:

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, 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 more than one tablet has been forgotten, a non-hormonal contraceptive measure should be used until the next usual withdrawal bleeding will occur.

If the usual withdrawal bleeding fails to appear following the forgotten intake, pregnancy must be excluded before starting with a new blister pack.

Procedure in case of vomiting or diarrhoea

In the event of vomiting or severe diarrhoea within the first 3-4 hours after taking Leonore, the active substances will possibly not be completely absorbed and additional contraceptive measures should be used. Furthermore, the same procedures should be used as recommended in case of a forgotten tablet. If the user does not wish to deviate from her normal rhythm of taking the tablets, she must take the replacement tablet from another blister pack. In the event of persistent or recurring gastrointestinal disorders, additional non-hormonal contraceptive measures should be used.

Change the starting day of withdrawal bleeding or to delay withdrawal bleeding

To delay withdrawal bleeding, the user should immediately continue taking the tablets of the next pack Leonore, without a tablet-free interval. The withdrawal bleeding can be delayed for as long as desired until the end of the second blister. During this time, breakthrough bleeding or spotting may increasingly occur. After the regular 7-day tablet-free period, the use of Leonore 0,1 mg/0,02 mg may be continued as usual.

If the woman wants to change the starting day or her withdrawal bleeding 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).

4.3 Contraindications

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

- Presence or risk of venous thromboembolism (VTE)
 - o Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
 - o 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
 - o Major surgery with prolonged immobilisation (see section 4.4)
 - o 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)
 - o Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
 - o Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
 - o Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).

- o History of migraine with focal neurological symptoms.
- o 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
- existing or previous pancreatitis if this is associated with severe hypertriglyceridaemia,
- Existing or previous severe liver disease, for as long as liver function has not normalised (also Dubin-Johnson and Rotor syndrome),
- Existing or previous hepatic tumours (benign or malignant),
- Known or suspected sex-hormone-dependent malignant tumours (e.g. of the genital organs or the breast) if these are influenced by sex hormones
- Undiagnosed vaginal bleeding,
- Undiagnosed amenorrhoea,
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of Leonore 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 Leonore should be discontinued.

- Vascular 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 Leonore should be taken after a discussion with the woman to ensure she understands the risk of VTE with Leonore, 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).

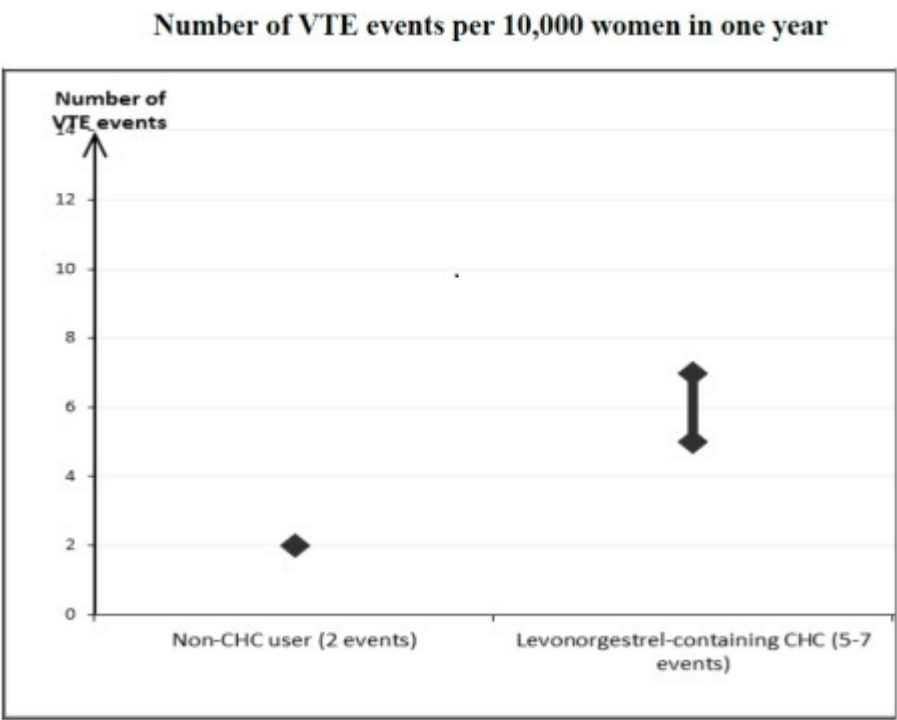
It is estimated that out of 10,000 women who use a CHC that contains levonorgestrel, about 6¹ will develop a VTE in a year.

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.

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



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).

Leonore 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)	<p>Risk increases substantially as BMI rises.</p> <p>Particularly important to consider if other risk factors also present.</p>
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma	<p>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</p>

<p>Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.</p>	<p>to avoid unintentional pregnancy.</p> <p>Antithrombotic treatment should be considered if Leonore has not been discontinued in advance.</p>
<p>Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50)</p>	<p>If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.</p>
<p>Other medical conditions associated with VTE</p>	<p>Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis) and sickle cell disease</p>
<p>Increasing age</p>	<p>Particularly above 35 years</p>

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). Leonore 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.

The possibility of anticoagulant therapy should also be taken into account. 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 behavior 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.

All women, in particular those over 35 years should have regular breast examinations while on the pill.

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 preexisting 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, hemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss, depressive mood.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the 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. However, diabetic women should be carefully monitored, particularly in the early stage of COC use.

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.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This medicinal product also contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

Medical examination/consultation

Prior to the initiation or reinstitution of Leonore 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 Leonore 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 diarrhea 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 Levonorgestrel/Ethinylestradiol, 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 bleed 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 the COC use is continued.

Stop intake with the intent of pregnancy

Women who stop taking Leonore because they wish to become pregnant, should be instructed that folic acid deficiency can lead to neural tube defects in the unborn child and that periconceptional supplementation with folic acid is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on Leonore

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 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 enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

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

When co-administered with COCs, many combinations of HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV 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 by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

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

Effects of Leonore on other medicinal products

Oral contraceptives may interfere with the metabolism of certain 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.

The need for insulin or oral antidiabetics can be altered due to influence on glucose tolerance.

The Summary of Product Characteristics of the prescribed medicinal products should be checked for potential interactions with Levonorgestrel/Ethinylestradiol.

- 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Leonore is not indicated during pregnancy.

Pregnancy should be excluded prior to the use of [Leonore](#). If pregnancy occurs during use of Leonore, this medicinal product must be discontinued immediately.

However, most epidemiological studies have revealed neither an increased risk of birth defects in children born to women taking contraceptive pills before 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 Leonore (see section 4.2 and 4.4).

Breast-feeding

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

Leonore has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The most common (> 10%) undesirable effects associated with use of Leonore are headache (including migraine), spotting and intracyclic menstrual bleeding.

Organ system	Incidence of adverse reactions			
	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)

Infections and infestations	Vaginitis, including candidiasis			
Immune system disorders			Allergic reactions, hypersensitivity	Angioedema, severe anaphylactic reactions with respiratory and circulatory symptoms
Metabolism and nutrition disorders		Changed appetite (increase or decrease), fluid retention	Impaired glucose tolerance	
Psychiatric disorders	Depressed mood, mood altered	Libido decreased	Libido increased	
Nervous system disorders	Nervousness, somnolence, vertigo, headache	Migraine		
Eye disorders	Dysopia		Contact lens intolerance	
Vascular disorders			Arterial thromboembolism (ATE), Venous thromboembolism (VTE)	
Gastrointestinal disorders	Nausea, abdominal pain	Diarrhoea, vomiting, abdominal cramps, flatulence		
Hepatobiliary disorders			Cholestatic icterus	
Skin and subcutaneous tissue disorders	Acne	Exanthema, chloasma (melasma) possibly persistent, hirsutism, alopecia, rash, urticaria	Erythema nodosum, erythema multiforme	
Reproductive system and breast disorders	Breast pain, breast tenderness, dysmenorrhoea, changed menstrual flow, changes in cervical transformation zone and secretion, amenorrhoea	Breast enlargement	Breast discharge, vaginal discharge	
Investigations	Weight increased	Rise in the blood pressure, changed lipid values in serum, including hypertriglyceridaemia	Weight decreased, decrease in the folic acid levels in the blood	

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.

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4 Special warnings and precautions for use:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours
- Crohn's disease, ulcerative colitis, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;

Furthermore, the following adverse reactions have been reported during use of combined oral contraceptives: The frequency of these adverse reactions cannot be calculated from the reports.

- optic nerve inflammation (may lead to partial or complete loss of vision),
- exacerbation of varicosis,
- pancreatitis in co-existent, severe hypertriglyceridaemia,
- gall bladder disease, including gall stones (combined oral contraceptives may lead to the occurrence of a gall bladder disease or worsen pre-existing gall bladder disease),
- haemolytic-uraemic syndrome,
- gestational herpes,
- otosclerosis,
- exacerbation of systemic lupus erythematosus,
- exacerbation of porphyria,
- exacerbation of Sydenham's chorea,
- exacerbation of depression,
- exacerbation of chronic-inflammatory intestinal diseases (Crohn's disease and ulcerative colitis).

The frequency of diagnosis of breast cancer is 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. For further information, see sections 4.3 and 4.4.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: <http://www.hpra.ie/>; E-mail: medsafety@hpra.ie.

4.9 Overdose

There have been no reports of serious effects from overdose. Symptoms of an overdose with oral contraceptives in adults and children may involve: nausea, vomiting, breast tenderness, drowsiness, abdominal pain, somnolence/fatigue; vaginal bleeding may occur in women and girls. There is no specific antidote. Symptomatic treatment should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combination

ATC code: G03AA07

Leonore coated tablets are a combination preparation for oral contraception (COC) and contain ethinylestradiol (EE) and levonorgestrel.

Ethinylestradiol

Mechanism of action

Ethinylestradiol is a potent oral synthetic oestrogen. Like the natural estradiol, ethinylestradiol has a proliferative action on epithelial tissues of female genital organs.

Pharmacodynamic effects

It stimulates the production of cervical mucus, reduces its viscosity and increases its threadability. Ethinylestradiol supports the growth of lactiferous ducts and inhibits lactation. Ethinylestradiol stimulates extracellular fluid retention. Ethinylestradiol affects parameters of lipid and carbohydrate metabolism, haemostasis, renin angiotensin aldosterone system and serum binding proteins.

Levonorgestrel

Mechanism of action

Levonorgestrel as the biologically active d-configuration of norgestrel has a very high gestagen potency.

Pharmacodynamic effects

The most specific progestative effect is secretory conversion of the endometrium. Levonorgestrel inhibits gonadotropin secretion in the anterior lobe of the pituitary gland. The antioviulatory dose is 0.06 mg daily.

Besides its gestagenic efficacy, levonorgestrel has also relatively potent anti-oestrogenic and low androgenic properties. The anti-oestrogenic component manifests itself in a significant decrease in the threadability of cervical mucus and disappearance of fern crystallization.

Comparable to progesterone, levonorgestrel has a thermogenetic effect.

Clinical studies have been conducted in a total of 2,498 women in the age range 18 – 40 years. The Pearl Index calculated on the basis of these studies was approximately 0,69 (95% confidence interval: 0,30 – 1,36) based on a total of 15,026 cycles.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption

Levonorgestrel is absorbed rapidly and almost completely after oral administration. Peak levonorgestrel serum concentrations of approximately 2.3 ng/ml are reached approximately 1.3 hours after administration. The bioavailability is almost 100%.

Distribution

Levonorgestrel is bound to serum albumin and sexual hormone binding globulin (SHBG). Only 1.1% of the total serum concentrations of the active substance is present as the free steroid. Approximately 65% is bound specifically to SHBG and approximately 35% non-specifically to albumin. The increase in SHBG induced by ethinylestradiol influences the relative distribution of levonorgestrel in various protein fractions. The induction of the binding protein leads to an increase in the fraction bound to SHBG and a decrease in the fraction bound to albumin. The apparent volume of distribution of levonorgestrel after administration of single dose is 129 l.

Biotransformation

Levonorgestrel is metabolised predominantly via reduction in $\Delta 4$ -3-oxo-group and hydroxylation at position 2a, 1b and 16b and subsequent conjugation. The majority of metabolites circulating in the blood are sulphates of 3a, 5b-tetrahydrolevonorgestrel, whereas they are excreted mainly in the form of glucuronides. A part of unchanged levonorgestrel also circulates as 17b-sulphate. Metabolic clearance may vary interindividually and this may partially explain the observed high fluctuations of the levonorgestrel concentrations in the users.

Elimination

The levonorgestrel serum levels fall in two phases. The terminal phase is characterised by a half-life of approximately 25 hours. Levonorgestrel and its metabolites are mainly excreted with the urine (40-68%) and approximately 16-48% with the faeces.

Steady-state conditions

In the course of continuous use of Levonorgestrel/Ethinylestradiol, the levonorgestrel serum level increases approximately three-fold and reaches steady-state conditions in the second half of the treatment cycle. The pharmacokinetics of levonorgestrel is influenced by the serum SHBG level, which increase approximately 1.5-1.6-fold during administration of oestradiol. For this reason, in steady-state conditions, the serum clearance rate and the volume of distribution are slightly reduced (0.7 ml/min/kg and approximately 100 l).

Ethinylestradiol

Absorption

After oral administration, ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of approximately 50 pg/ml are reached within 1 - 2 hours of administration of the tablet. During absorption and first pass through the liver ethinylestradiol is extensively metabolised, resulting in a mean oral bioavailability of approximately 45% (range of individual variation approximately 20 – 65%).

Distribution

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

Biotransformation

Ethinylestradiol undergoes presystemic conjugation both in the mucosa of the small intestine and in the liver. Ethinylestradiol is metabolised primarily by aromatic hydroxylation, in the course of which various hydroxylated and methylated metabolites are formed. These can be detected as free metabolites and glucuronide and sulphate conjugates in serum. Ethinylestradiol is subject to enterohepatic circulation.

Elimination

The serum ethinylestradiol levels fall in two phases with half-lives of approximately 1 hour and 10 - 20 hours, respectively.

Ethinylestradiol is not excreted in unchanged form. The metabolites are excreted via the urine and the bile in the ratio 4:6.

Steady-state conditions

In the course of continuous use of Levonorgestrel/Ethinylestradiol, the ethinylestradiol serum concentration increases approximately two-fold. On account of the daily administration and the variable half-life in the terminal phase of serum clearance, steady-state conditions are reached after approximately 1 week.

5.3 Preclinical safety data

The toxicity profiles of ethinylestradiol and levonorgestrel are well known. Because of pronounced species differences, results from experimental animal studies have only a limited predictive value for the use in humans.

In experimental animals, ethinylestradiol showed an embryo-lethal effect already at relatively low doses. Malformations of the urogenital tract and feminization of male fetuses were observed. Levonorgestrel showed an embryo-lethal effect

in animal experiments and, at high doses, a virilizing effect on female foetuses. Reproductive-toxicological studies in rats, mice and rabbits did not reveal any evidence of teratogenicity beyond the described effects on sexual differentiation.

Conventional non-clinical studies of chronic toxicity, genotoxicity and of the carcinogenic potential did not reveal special hazards of ethinylestradiol or levonorgestrel for humans except those already described in other sections of this summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Magnesium stearate
Maize starch
Povidone K25
Talc

Tablet coating
Calcium carbonate
Carnauba wax
Macrogol 6000
Povidone K 90
Sucrose
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister with 21 coated tablets.

Calendar packs with 1 x 21, 3 x 21, 6 x 21, and 50 x 21 coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/127/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 29th February 2008

10 DATE OF REVISION OF THE TEXT

June 2016