Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levonorgestrel/ Ethinylestradiol 150 micrograms/30 micrograms coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 150 micrograms levonorgestrel and 30 micrograms ethinylestradiol.

Excipients with known effect:
Each coated tablet contains 42.46 mg lactose (as monohydrate), 28 mg sucrose and 0.013 mg soya (in lecithin).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablets.

Round (6 mm), biconvex, yellow, coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

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

4.2 Posology and method of administration

Method of administration

Oral use.

Posology

How to take Levonorgestrel/Ethinylestradiol

Combined oral contraceptives have a failure rate of approximately 1% per year, when they are taken correctly. The failure rate may increase when tablets are forgotten or not taken correctly.

The tablets must be taken in the order indicated on the blister, every day at approximately the same time, with some liquid if necessary. One tablet must be taken daily for 21 consecutive days. Each subsequent pack must be started after a 7-day tablet-free interval. During this interval a withdrawal bleed usually occurs. This bleeding usually starts 2 to 3 days after the last tablet and may not have ended before the start of the next pack.

How to get started with Levonorgestrel/Ethinylestradiol

• No prior hormonal contraceptive (in the previous month)

Tablet intake must begin on the first day of the woman's natural cycle (i.e. the first day of menstruation). Starting on days 2–5 is allowed, but during the first cycle an additional barrier method is recommended during the first 7 days of tablet intake.

• Switching to another combined hormonal contraceptive (combined oral contraceptive / COAC), vaginal ring, transdermal patch

It is preferable that woman should start Levonorgestrel/Ethinylestradiol on the day after taking the last active tablet of her previous COAC, but at the latest on the day after the usual tablet-free interval. In the case of vaginal ring or patch use, the woman should preferably start on the day of removal of the last ring or patch of a cycle pack, but at the latest the day the next application would be due.

• Switching after a progestogen-only method (mini-pill, injection, implant) orof a progestogen-releasing intrauterine system (IUS)

The woman may switch:

- from a mini-pill whenever she wishes
- from an implant or an IUD on the day of removal,
- from an injectable preparation when the next injection is scheduled.

but in all these cases, it is advised to use an additional barrier method for the first 7 days of tablet-taking.
• After a first-trimester abortion

The woman may start immediately. In this case, she does not need any additional contraceptive measures.

• After childbirth or after an abortion in the second trimester

For women who are breastfeeding, see section 4.6

It is recommended to start Levonorgestrel/Ethinylestradiol between day 21 and 28 after delivery or after an abortion in the second trimester. If a woman starts later, she should be advised to use an additional barrier method for the first 7 days of tablet-taking. . If sexual intercourse has already taken place, pregnancy must be ruled out before actually starting the COAC, or the woman must wait for her first menstruation.

What to do after forgetting tablets
If the user is **less than 12 hours late** in taking a tablet, the contraceptive reliability is not reduced. The woman should take the tablet as soon as she remembers and take subsequent tablets at the usual times.

If **more than 12 hours late** in taking a tablet, the contraceptive reliability may be reduced.
In the event of forgotten tablets, the following two basic principles can be followed:
1. Taking the tablets must never be interrupted for longer than 7 days.
7 consecutive days of tablet intake are necessary for adequate suppression of the hypothalamus-pituitary-ovarian axis.

Consequently, the following advice applies in daily practice:

• Week 1.

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She should then continue taking the next tablets at her usual time. Furthermore, a barrier method such as a condom must be used for the next 7 days. If sexual intercourse has taken place during the 7 days prior to the missed dose, the possibility of pregnancy should be considered. The more tablets missed and the closer they are to the normal tablet-free interval, the higher the risk of pregnancy.

• Week 2.
The user should take the last forgotten tablet as soon as she remembers, even if this means taking two tablets at the same time. She should then continue taking the subsequent tablets at her usual time.
Provided that the woman has taken her tablets correctly during the 7 days prior to the first forgotten tablet, there is no need for additional contraceptive precautions. However, if this is not the case, or if she has forgotten more than one tablet, the woman should be advised to take additional precautions for 7 days.

• Week 3.
The risk of reduced reliability is high due to the approaching tablet-free interval.

However, a reduction in contraceptive protection can still be prevented by adjusting the tablet intake schedule. Consequently, if the woman adheres to one of the following two options, no additional
contraceptive precautions are required, provided that she has taken all tablets correctly for 7 days prior to the first missed tablet. If this is not the case, the woman should be advised to follow the first option and also take additional precautions for the following 7 days.

1. The user should take the missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She should then continue taking the next tablets at her usual time. The next blister pack should be started as soon as the previous one is empty, i.e., without a break between blister packs. The user may not experience withdrawal bleeding before the end of the second blister pack, but she may experience spotting or breakthrough bleeding during the days she takes the tablets.

2. The woman may also be advised to stop taking the tablets from the opened blister pack. She should then take a tablet free interval of no more than 7 days (including the days she forgot tablets) and subsequently continue with the next blister pack.

If the woman has forgotten tablets and subsequently does not have a withdrawal bleeding in the first normal tablet-free interval, the possibility of pregnancy should be considered

What to do in case of gastrointestinal disorders

In the event of severe gastrointestinal disorders, absorption may not be complete, and additional contraceptive measures should be taken.

If vomiting or severe diarrhea occurs within 3-4 hours after taking a tablet, the same advice applies as for missed tablets, as given in the section "What to do after missed tablets". If the woman does not wish to change her normal tablet intake schedule, she must take the necessary extra tablet(s) from another blister pack.

How to postpone or shift the monthly bleeding

To postpone a monthly bleeding, the woman should continue with the next blister pack of Microgynon 30 without a tablet-free period. The postponement can be continued for as long as desired, until the end of the second blister pack.
During the extension, the woman may experience breakthrough bleeding or spotting. After the usual 7-day tablet-free period, the normal intake of Microgynon 30 is then resumed.

To shift menstruation to a different day of the week than the woman is accustomed to with the current schedule, she can be advised to shorten the next tablet-free interval by the desired number of days. The shorter the interval, the greater the risk that no withdrawal bleeding will occur and that breakthrough bleeding and spotting will occur during the second blister pack (just as with postponing menstruation).

Additional information regarding special populations

Paediatric population
Levonorgestrel/Ethinylestradiol is only indicated after the first period.

Geriatric population
Not applicable. Levonorgestrel/Ethinylestradiol is not indicated for post-menopause use.

Patients with hepatic impairment
Levonorgestrel/Ethinylestradiol is contraindicated in women with severe liver disease. See section 4.3.

Patients with renal impairment
Levonorgestrel/Ethinylestradiol has not been studied specifically in patients with renal impairment. Based on the available data, adapting the treatment for this patient population is not necessary.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following situations. Should any of these occur for the first time while using the CHC, the product should be discontinued immediately.

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Presence or risk of venous thromboembolism (VTE)
- Venous thromboembolism – presence of VTE (patient treated with anticoagulants) or history of VTE (e.g., deep vein thrombosis [DVT] or pulmonary embolism [PE])
- Known inherited or acquired predisposition to venous thromboembolism, such as activated protein C (PCa) resistance (including Factor V Leiden), antithrombin III deficiency, protein C deficiency, protein S deficiency
- Major surgery with prolonged immobilisation (see section 4.4)
- 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 – presence or history of arterial thromboembolism (e.g., myocardial infarction) or prodromes (e.g., angina pectoris)
    - Cerebrovascular disease – presence or history of stroke or prodromes (e.g., transient ischemic attack [TIA])
    - Known hereditary or acquired predisposition to arterial thromboembolism, such as hyperhomocysteinaemia or the presence of antiphospholipid antibodies (anti-cardiolipin antibodies, lupus anticoagulant)
    - History of migraine with focal neurological signs
    - High risk of arterial thromboembolism due to the presence of multiple risk factors (see section 4.4) or a severe risk factor, such as:

        - diabetes with vascular symptoms
        - severe high blood pressure
        - severe dyslipoproteinaemia.

- Severe liver disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Presence or suspicion of sex steroid dependent malignancies (e.g., genitals or breasts).
- Undiagnosed vaginal bleeding.
- Pregnancy or suspicion of pregnancy.

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

4.4 Special warnings and precautions for use

Warnings
If the patient has any of the conditions or risk factors listed below, the suitability of Levonorgestrel/ Ethinylestradiol treatment should be discussed with her.

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 Levonorgestrel/Ethinylestradiol should be discontinued.

Risk of venous thromboembolism (VTE)
The risk of VTE is higher in women who use a combined hormonal contraceptive (CHC) compared to women who do not. **The decision to use Levonorgestrel/Ethinylestradiolshould only be taken after consultation with the patient to ensure that she understands the risk of VTE associated with Levonorgestrel/Ethinylestradiol, the influence of her current risk factors on this risk and the fact that the risk of VTE is greatest during the first year of use. Some data also indicate an increased risk when resuming a CHC after an interruption of 4 weeks or more.**

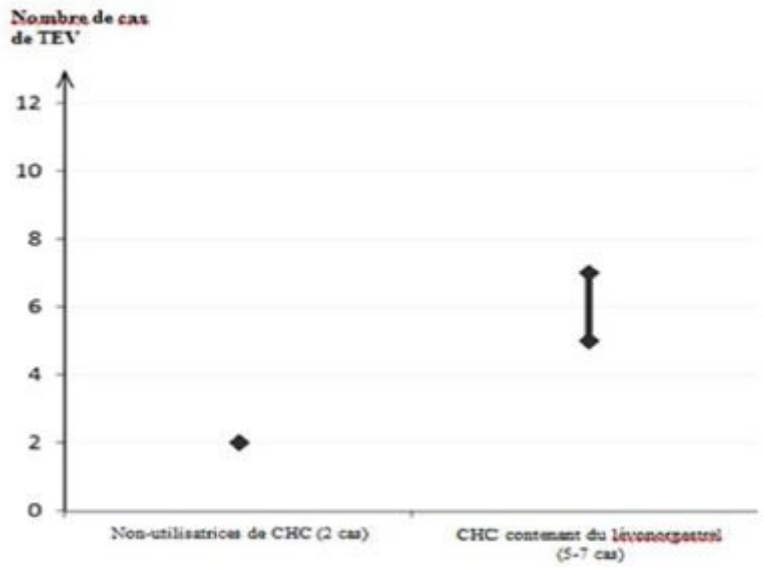
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below)

Epidemiological studies in women who use low dose combined oral contraceptives (<50 µg ethinylestradiol) have found that out of 10,000 women between about 6 and 12 will develop a VTE in one year.

Out of 10,000 women who use a levonorgestrel-containing CHC about 6 will develop a VTE in one year. The number of VTEs per year with low dose CHCs is fewer than the number expected in women during pregnancy or in the postpartum period.

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

Number of VTE cases per 10 000 women over a one-year period



Midpoint of the range 5-7 per 10,000 women years based on a relative risk, for CHCs containing levonorgestrel versus no CHC use, of approximately 2.3 to 3.6.

Extremely rarely, cases of thrombosis have been reported in CHC users in other blood vessels, e.g., hepatic, mesenteric, renal, cerebral 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).

Levonorgestrel/Ethinylestradiol is contraindicated in women with multiple risk factors which put them at high risk of venous thrombosis (see section 4.3). When a woman has more than one risk factor, the increased risk may be higher than the sum of the risks associated with each factor taken individually – in this case, the overall risk of VTE should be considered. If the benefit/risk ratio is considered unfavourable, the CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index greater than 30 kg/m^2)	Higher BMI greatly increases the risk. This is especially important to consider if other risk factors are present.
Prolonged immobilisation, major surgery, any surgery on the legs or pelvis, neurosurgery or major trauma Note: Temporary immobilisation, including air travel >4 hours, may also be a risk factor for VTE, especially 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. Anti-thrombotic treatment should be considered if Levonorgestrel/Ethinylestradiol has not been discontinued in advance.
Family history (venous thromboembolism occurring in siblings or in a	In case of suspected hereditary predisposition, the

relative, especially at a relatively young age, i.e., before 50 years of age)	woman should be referred to a specialist for advice before any decision concerning CHC use.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel diseases (Crohn's disease or ulcerative colitis) and sickle cell disease
Age	Especially over 35 years of age

There is no consensus on the possible role played by varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism during pregnancy, and in particular during the 6 weeks of the puerperal period, should be taken into account (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 a leg and/or foot or along a vein in the leg;
- pain or tenderness in one leg, which may only be felt when standing or walking;
- feeling of warmth, redness or change in the skin colour of the affected leg.

Symptoms of pulmonary embolism (PE) can include:
- sudden and unexplained onset of shortness of breath or rapid breathing;
- sudden cough, which may be associated with haemoptysis;
- acute chest pain;
- severe light headedness or dizziness;
- fast or irregular heartbeats.

Some of these symptoms (e.g., "shortness of breath", "cough") are non-specific and may be misinterpreted as signs of more frequent or less severe events (e.g., respiratory infections).

Other signs of a vascular blockage may include: sudden pain, swelling, and slightly bluish discolouration of one extremity.

If the blockage occurs in the eye, symptoms may begin as painless blurred vision which may progress to loss of vision. In some cases, vision loss can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have shown an association between the use of CHCs and an increased risk of arterial thromboembolism (myocardial infarction) or cerebrovascular accident (e.g., transient ischaemic attack, stroke). Arterial thromboembolic events can 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). [Invented name] 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).
When a woman has more than one risk factor, the increased risk may be higher than the sum of the risks associated with each factor taken individually – in this case, the overall risk should be considered. If the benefit/risk ratio is considered unfavourable, the CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	**Comment**
Age	Especially over 35 years of age
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 greater than 30 kg/m^2)	Higher BMI greatly increases the risk. This is especially important to consider in women with other risk factors.
Family history (arterial thromboembolism occurring in siblings or in a relative, especially at a relatively young age, i.e., before 50 years of age)	In case of suspected hereditary predisposition, the woman should be referred to a specialist for advice before any decision concerning CHC use.
Migraine	Increased frequency or severity of migraine headaches with CHC use (which may be a prodrome of a cerebrovascular event) may be grounds for immediate discontinuation of the CHC.
Other medical conditions associated with vascular adverse events	Diabetes, hyperhomocysteinaemia, heart valve disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

Women should be advised that, should these symptoms occur, they should seek urgent medical attention and inform the healthcare professional that they are 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 onset of difficulty walking, dizziness, loss of balance or coordination;
- sudden onset of confusion, difficulty speaking or understanding;
- sudden onset of difficulty seeing in one or both eyes;
- sudden, severe or prolonged headache, without known cause;
- loss of consciousness or fainting with or without a seizure.

Temporary symptoms suggest a transient ischaemic attack (TIA).
Symptoms of myocardial infarction (MI) can include:
- pain, discomfort, pressure, heaviness, tightness 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;
- fast or irregular heartbeats.

Tumours
The main risk factor for cervical carcinoma is persistent HPV infection. Some epidemiological studies have indicated that prolonged use of CHCs may also contribute to this increased risk, but debate remains as to the degree to which this observation is attributable to interfering effects, e.g., sexual behaviour, including use of barrier contraceptive methods and other factors such as human papillomavirus (HPV).

A meta-analysis of 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of being diagnosed with breast cancer in women using a CHC. The additional risk gradually disappears over the 10 years following CHC discontinuation. Since breast cancer is rare in women under 40 years of age, the incremental number of breast cancer diagnoses in women who use or have used a CHC in the recent past is small compared to the lifetime risk of breast cancer. These studies do not provide evidence of causation. The type of additional risk observed could be due to an earlier diagnosis of breast cancer in CHC users, the biological effects of CHCs, or a combination of both. Breast cancers diagnosed in CHC users tend to be less advanced clinically than those diagnosed in women who have never used CHCs.

In rare cases, benign and even more rarely malignant liver tumours have been reported in CHC users. In isolated cases, these tumors have caused life-threatening intra-abdominal bleeding. A hepatic tumour should be considered in the differential diagnosis in case of severe upper abdominal pain, increased liver volume or signs of intra-abdominal haemorrhage in a CHC user.

Malignant tumors can be life-threatening or fatal.

Other situations
Women with hypertriglyceridaemia, or a family history of hypertriglyceridaemia may be at increased risk of pancreatitis when using CHCs.

Although slight increases in blood pressure have been reported in many CHC users, clinically significant increases are rare. Only in these rare cases is an immediate discontinuation of CHC use warranted. If, during the use of a CHC in patients with pre-existing hypertension, persistently elevated blood pressure values or a significant increase in blood pressure does not respond sufficiently to antihypertensive therapy, the CHC should be discontinued. Where considered appropriate, CHC use may be resumed if blood pressure normalises on antihypertensive therapy.

Onset or worsening of the following conditions has been reported, both during pregnancy and during CHC use, but there is no definite evidence of a link with CHC intake: jaundice and/or pruritus due to cholestasis; cholelithiasis; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gravidarum; hearing loss due to otosclerosis.

Exogenous oestrogens can trigger or aggravate the symptoms of hereditary and acquired angioedema.

Acute or chronic impairment of liver function may necessitate discontinuation of the CHC until liver function parameters return to normal. If cholestatic jaundice and/or pruritus secondary to cholestasis occurs for the first time during pregnancy or prior use of sex steroids, the CHC should be discontinued.

Although CHCs may have an effect on peripheral insulin resistance and glucose tolerance, the need to modify the treatment regimen of diabetic women using low-dose CHCs (containing <0.05 mg ethinyl estradiol) has not been proven. However, women with diabetes should be closely monitored when taking CHCs, especially at the start of CHC use.

Depression and depressed mood are well known adverse reactions associated with the use of hormonal contraceptives (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 doctor in case of mood swings and depressive symptoms, including shortly after starting treatment.

Worsening of Crohn's disease and ulcerative colitis has been associated with CHC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a predisposition to chloasma should avoid exposure to the sun or ultraviolet rays while using CHCs.

Examination and medical consultation
Prior to initiation or resumption of treatment with Levonorgestrel/Ethinylestradiol, a full medical history (including family history) should be taken and pregnancy should be excluded. Blood pressure should be measured and a physical examination performed, bearing in mind the contraindications (see section 4.3) and warnings (see section 4.4). It is important to draw the attention of patients to information relating to venous and arterial thrombosis, including the risk associated with Levonorgestrel/Ethinylestradiol compared to other CHCs, symptoms of VTE and ATE, known risk factors and what to do if thrombosis is suspected.

Patients should also be instructed to read the package leaflet carefully and follow the advice provided. The frequency and nature of the examinations must be defined on the basis of the recommendations in force and adapted to each patient.

Patients should be advised that hormonal contraceptives do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Decreased reliability
The reliability of CHCs may be reduced in the event of missed tablets, vomiting or diarrhoea (Section 4.2) or concomitant use of other medicinal products (section 4.5).

Menstrual Changes

Missed menstruation: Occasionally, withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is very unlikely. If withdrawal bleeding fails to occur at the end of a second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

Intermenstrual bleeding: 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. This may include curettage.

Excipient(s) with known effect

Levonorgestrel/Ethinylestradiol 150 micrograms/30 micrograms Coated Tablets also contains lactose, sucrose and soya.

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Soya: If the patient is allergic to soya, do not take this medicinal product (see section 4.3)

4.5 Interaction with other medicinal products and other forms of interaction

Note: Consult the prescribing information of concomitant medications to identify possible interactions.

Effects of other medicinal products on Levonorgestrel/Ethinylestradiol
Interactions may occur with medicinal products that induce microsomal enzymes, which may lead to accelerated clearance of sex hormones and the occurrence of intercurrent bleeding and/or contraceptive failure.

Women taking any of these medicinal products should temporarily use a barrier method in addition to the CHC, or switch to another method of contraception. The barrier method should be used throughout the duration of concomitant treatment and up to 28 days after discontinuation of this treatment.
If the period during which the barrier method is to be used extends beyond the end of the tablets in the CHC pack, the next pack should be started immediately, without observing the usual tablet-free interval.

Substances which increase CHC clearance (reduced CHC efficacy by enzyme induction), e.g.:
Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort.

Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After discontinuation of treatment, enzyme induction may be maintained for approximately 4 weeks.

Substances that have a variable effect on the CHC clearance, e.g.:
Many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of oestrogen or progesterone when co-administered with CHCs. In some cases, these changes may be clinically significant.

Substances which decrease the CHC clearance (enzyme inhibitors)
Strong and moderate CYP3A4 inhibitors, such as azole antifungals (e.g., itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem, and grapefruit juice may increase plasma concentrations of oestrogen or progesterone, or both.

Etoricoxib, administered in doses of 60-120 mg per day, increases plasma concentrations of ethinylestradiol by a factor of 1.4-1.6, respectively, when used concomitantly with a combined hormonal contraceptive containing 0.035 mg of ethinylestradiol.

Effects of CHCs on other medicinal products
Oral contraceptives can influence the metabolism of certain other medicinal products. As a result, plasma and tissue concentrations may either increase (e.g., ciclosporin) or decrease (e.g., lamotrigine).

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. In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol

resulted in no or only slightly increased plasma concentrations of CYP3A4 substrates (e.g., midazolam), while plasma concentrations of CYP1A2 substrates may see a slight (e.g., theophylline) or moderate (e.g., melatonin and tizanidine) increase.

Pharmacodynamic interactions
In clinical trials in patients treated for hepatitis C virus (HCV) infection and receiving medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, increases in transaminase (ALT) greater than 5 times the upper limit of normal (ULN) have been observed, significantly more frequent in women using medicinal products containing ethinylestradiol, such as combined hormonal contraceptives (CHCs). Additionally, in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, increases in ALT have been observed in women using ethinylestradiol-containing medicinal products such as CHCs (see section 4.3).

Therefore, users of Levonorgestrel/Ethinylestradiol should change their method of contraception (e.g., progestogen-only contraceptive or non-hormonal methods) before starting treatment with these medicinal products. Levonorgestrel/Ethinylestradiol can be restarted 2 weeks after the end of treatment with these medicinal products.

Other forms of interactions

- Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins e.g., corticosteroid-binding globulin and lipid/lipoprotein fractions, carbohydrate metabolism parameters and those of coagulation and fibrinolysis. These variations generally remain within normal laboratory limits.

4.6 Fertility, pregnancy and lactation

Pregnancy
Levonorgestrel/Ethinylestradiol is not indicated during pregnancy. If pregnancy occurs during treatment with Levonorgestrel/Ethinylestradiol, this medicinal product should be discontinued. The numerous epidemiological studies have however revealed neither an increased risk of congenital anomalies in children whose mothers had used a CHC before pregnancy, nor a teratogenic effect when CHCs had been taken inadvertently at the start of pregnancy.

The increased risk of VTE in the postpartum period should be considered when resuming Levonorgestrel/Ethinylestradiol (see sections 4.2 and 4.4).

Breast-feeding
Lactation can be affected by CHCs because they can reduce the volume of breast milk and alter its composition. Consequently, CHCs are generally not recommended until the child is completely weaned. Small amounts of contraceptive steroids and/or their metabolites may be excreted in milk. These amounts can have an effect on the child.

4.7 Effects on ability to drive and use machines

No studies on effects on ability to drive and use machines have been performed. Levonorgestrel/Ethinylestradiol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most reported undesirable effects with Levonorgestrel/Ethinylestradiol are: nausea, abdominal pain, weight gain, headache, depressed mood, mood swings, breast pain, breast tenderness. These undesirable effects occur in ≥1% of users.

Serious adverse events are arterial thromboembolism and venous thromboembolism.

Table of undesirable effects
The following undesirable effects have been reported during treatment with Levonorgestrel/Ethinylestradiol:

MedDRA	Common	Uncommon	Rare	Not known

system organ class	**(≥1/100 to <1/10)**	**(≥1/1 000 to <1/100)**	**(≥1/10 000 to <1/1 000)**	**(cannot be estimated from the available data)**
Eye disorders			contact lens intolerance	
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhoea		
Immune system disorders			hypersensitivity	exacerbation of symptoms of hereditary and acquired angioedema
Investigations	weight gain		weight loss	
Metabolism and nutrition disorders		fluid retention		
Nervous system disorders	headache	migraine		
Psychiatric disorders	depressed mood, mood swings	decreased libido	increased libido	
Reproductive system and breast disorders	pain in the breasts, breast tenderness	breast enlargement	breast secretion, vaginal discharge	
Skin and subcutaneous tissue disorders		rash, hives	erythema nodosum, erythema multiforme	
Vascular disorders			arterial thromboembolism (ATE), venous thromboembolism (VTE)**	

*The table lists the most appropriate MedDRA term to describe a given undesirable effect. Synonyms or related conditions are not listed, but should also be considered.

** - Estimated frequency based on epidemiological studies including a group of combined hormonal contraceptives.
- The terms "arterial thromboembolism (ATE), venous thromboembolism (VTE)" include the following medical terms: peripheral deep vein occlusion, thrombosis and pulmonary vascular embolism/occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction, and stroke not defined as haemorrhagic.

Description of selected undesirable effects

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; this is discussed in more detail in section 4.4.

Undesirable effects with a very low frequency or delayed onset of symptoms which are considered to be associated with the combined hormonal contraceptive group are described below (see also sections 4.3 and 4.4):

Tumours

- The frequency of breast cancer diagnosis is slightly increased in women using oral contraceptives. Because breast cancer is rare in women under 40 years of age, the excess number of diagnosed cases is small compared to the overall risk of breast cancer. The causal link to CHC use has not been established. For more information, see sections 4.3 and 4.4.
- Liver tumours (benign or malignant).

Other conditions

- Women with hypertriglyceridaemia (increased risk of pancreatitis with CHC use).
- Arterial hypertension.
- Onset or worsening of conditions for which a link to CHC use has not been established with certainty: jaundice and/or pruritus associated with cholestasis; cholelithiasis; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; hearing loss due to otosclerosis.
- Liver function disorders.
- Changes in glucose tolerance or effect on peripheral insulin resistance.
- Crohn's disease, ulcerative colitis.
- Chloasma.

Interactions
Intercurrent bleeding and/or contraceptive failure may result from interactions between other medicinal products (enzyme inducers) and 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. Website: www.hpra.ie.

4.9 Overdose

There are no reports of serious deleterious effects due to overdose. Symptoms that may occur in this case are: nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may occur in girls who have not yet had their first period if they take this medicine by mistake. There are no antidotes and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, Progestogens and oestrogens, fixed combinations
ATC Code: G03AA07

Levonorgestrel/Ethinylestradiol is an oestrogen-progestogen combination which acts by inhibiting ovulation by suppression of the mid-cycle surge of luteinizing hormone, the inspissation of cervical mucus so as to constitute a barrier to sperm, and the rendering of the endometrium unreceptive to implantation.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption
Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of approximately 3-4 ng/mL are reached approximately 1 hour after a single dose. The bioavailability of levonorgestrel is almost complete after oral administration.

Distribution
Levonorgestrel is bound to serum albumin and to SHBG (sex hormone binding globulin). Only 1.3% of the total serum levonorgestrel concentration is present as the free steroid, about 64% is specifically bound to SHBG and about 35% is not specifically bound to albumin. The ethinyl estradiol-induced increase in SHBG influences the distribution of levonorgestrel which is bound to serum proteins and induces an increase in the fraction bound to SHBG and a decrease in the fraction bound to albumin. The apparent volume of distribution of levonorgestrel is approximately 184 L after single administration.

Biotransformation

Levonorgestrel is largely metabolised. The main metabolites in plasma are the conjugated and unconjugated forms of 3α, 5β-tetrahydrolevonorgestrel. *In vitro* and *in vivo* studies show that CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel. The metabolic elimination rate for serum is approximately 1.3 to 1.6 mL/min/kg.

Elimination
Serum levonorgestrel levels decline in 2 phases. The terminal excretion phase is characterised by a half-life of approximately 20-23 hours. Levonorgestrel is not eliminated unchanged. Its metabolites are excreted in a urinary to biliary ratio of approximately 1:1. The elimination half-life of the metabolites is approximately 1 day.

Steady state
After daily administration, serum drug levels increase by a factor of 3 to 4 and reach steady-state concentration during the second half of a treatment cycle. The pharmacokinetic properties of levonorgestrel are influenced by SHBG levels which increase by a factor of 1.7 after daily administration of Levonorgestrel/Ethinylestradiol *per os*. This effect induces a decrease in the elimination rate to about 0.7 mL/min/kg at steady state.

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Serum peaks of approximately 95 pg/mL are reached after 1-2 hours. During absorption and the first hepatic pass, ethinylestradiol is extensively metabolised, which results in an average bioavailability of approximately 45% with a large interindividual variability of approximately 20 to 65%.

Distribution
Ethinylestradiol is highly but not specifically bound to serum albumin (approximately 98%) and induces increased serum concentrations of SHBG. An apparent distribution volume of approximately 2.8-8.6 L/kg has been determined.

Biotransformation
Ethinylestradiol undergoes presystemic conjugation, both in the mucosa of the small intestine and in the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed, and these metabolites are present as free metabolites and glucuronide/sulphate conjugates. The reported metabolic elimination rate is 2.3-7 mL/min/kg.

Elimination
Serum ethinylestradiol levels decline in 2 phases of distribution, characterised by half-lives of approximately 1 hour and 10-20 hours, respectively. Unchanged ethinyl estradiol is not eliminated; ethinylestradiol metabolites are eliminated in a urinary to biliary ratio of 4:6. The elimination half-life of the metabolites is approximately 1 day.

Steady state
Serum ethinylestradiol concentrations increase slightly after daily oral administration of Levonorgestrel/Ethinylestradiol. Peak concentrations at the end of a treatment cycle are approximately 114 pg/mL. Due to the variable half-life of the terminal serum distribution phase and daily intake, steady-state serum concentrations are reached after approximately one week.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. A carcinogenic effect can be produced in certain strains of mice and rats when progestogens, estrogens and combinations of the hormones are given in high doses throughout their life span. The susceptibility to tumour induction by hormonal contraceptives is not consistent in different strains of mice and rats and such studies have not provided useful predictive information of the potential carcinogenicity in women.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets Core:
Maize starch
Pregelatinised starch (maize)
Povidone

Lactose monohydrate
Anhydrous colloidal silica
Magnesium stearate

Film-Coating:
Polyvinyl alcohol, partially hydrolysed (E1203)
Titanium dioxide (E171)
Talc (E553b)
Macrogol (E1521)
Lecithin (soya)
Sucrose
Acacia gum
Maize starch
Calcium carbonate
Povidone
Polysorbate 80
Ferric oxide – yellow
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 storage conditions.

6.5 Nature and contents of container

Alu//PVDC blister.
Each carton contains either 1 or 3 blister packs. Each blister pack contains 21 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited
12 Crowe Street
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Co. Louth
A91 NN29
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22865/016/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 21/08/2026

10 DATE OF REVISION OF THE TEXT