SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gedarel 20/150 microgram film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 micrograms ethinylestradiol and 150 micrograms desogestrel

Excipient with known effect: 64.3 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Slightly yellow, round shaped, biconvex film-coated tablets of about 6 mm diameter, with P9 sign on one side and RG sign on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

The decision to prescribe Gedarel should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Gedarel 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 Gedarel
Tablets must be taken in the order directed on the package every day at about the same time. One tablet is taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval; during which time a withdrawal bleed usually occurs. This usually

starts on day 2-3 day after the last tablet and may not have finished, before the next pack is started.

How to start Gedarel
No preceding hormonal contraceptive use [in the past month]
The tablet intake must be started on day 1 of the normal menstrual cycle (i.e. on the first day on which the woman has a menstrual bleeding). Tablet intake is also allowed to start on day 2-5, but during the first cycle concurrent use of a barrier method for the first 7 days of tablet intake is advisable.

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), combined contraceptive vaginal ring or transdermal patch)
The woman should start taking Gedarel on the day after the last active tablet (the last tablet containing the active substance) of her previous COC, but at the latest on the day following the usual tablet-free interval or following the last placebo tablet (tablet containing no active substance) of her previous COC.
In case a vaginal ring or a transdermal patch has been used, the woman should start using Gedarel preferably on the day of removal.
The woman may also start using Gedarel on the day the new vaginal ring or a transdermal patch would have been due, but no later than this day.

If the woman has been using her previous contraception method regularly and correctly and if the woman is not pregnant she may also switch from her previous hormonal contraception on any day of the cycle.

The hormone-free period from the previous contraception method must not be extended for longer than recommended.

Not all administration methods of hormonal contraception (transdermal patch, vaginal ring) is necessarily marketed in all EU countries.

Changing from progestogen only products (progestogen-only-pills, injection, implant or a progestogen-releasing intrauterine system (IUS))

The woman can change from progestogen-only pills on any day (changing from implant or IUS on the day of its removal; changing from injection when the next injection should have been given) but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

After abortion in the 1st trimester
Tablet intake should start immediately. In this case no further contraceptive measures are necessary.

After delivery or abortion in the 2nd trimester
For breast-feeding women - see section 4.6.
The woman should be advised to start the pill on day 21-28 after delivery or abortion in the 2nd trimester. She should be advised to use a barrier method concurrently during the first 7 days of tablet intake if she starts the pill later. In case she has already had intercourse, pregnancy should be excluded or she should wait for her first menstrual bleeding before she starts taking Gedarel.

Missed tablets
If the tablet intake is forgotten for less than 12 hours, contraceptive protection is not reduced. The woman should take the forgotten tablet as soon as she remembers, and the remaining tablets are taken as usual.

If the tablet intake is forgotten for more than 12 hours, contraceptive protection may be reduced. The following two basic rules should be considered in case of forgotten tablets:

1. Continuous tablet intake must not be interrupted for longer than a period of 7 days.
2. 7 days of uninterrupted tablet intake are required to achieve sufficient suppression of the hypothalamus-pituitary-ovarian-axis.

Thus, the following advice may be given for daily practice:

Week 1

The woman should take the last forgotten tablet as soon as she remembers, even if this means that she has to take 2 tablets at the same time. Then, she continues taking the tablets at the usual time of the day. She should concurrently use a barrier method, e.g. a condom, for the next 7 days. If intercourse has taken place during the preceding 7 days, the possibility of pregnancy should be considered. The more tablets are forgotten and the closer they are to the regular tablet-free period, the higher the risk of pregnancy is.

Week 2

The woman should take the last forgotten tablet as soon as she remembers, even if this means that she has to take 2 tablets at the same time. Then, she continues taking the tablets at the usual time of the day. Provided that the tablets have been taken in a correct manner during the 7 days preceding the forgotten tablet, it is not necessary to take further contraceptive measures. However, if this is not the case, or if more than 1 tablet has been forgotten, the woman should be advised to use another contraceptive method for 7 days.

Week 3

The risk of reduced contraceptive protection is imminent due to the forthcoming 7-day tablet-free period. However, this risk may be prevented by adjusting tablet intake. Thus, it is not necessary to take further contraceptive measures if one of the two alternatives below is followed, provided that all tablets have been taken in a correct manner during the 7 days preceding the forgotten tablet. If this is not the case, the woman should be advised to follow the first of the two alternatives and concurrently use another contraceptive method for the next 7 days.

1. The woman should take the last forgotten tablet as soon as she remembers even if it means that she has to take 2 tablets at the same time. Then she continues taking the tablets at the usual time of the day. She will begin taking the next pack immediately after taking the last tablet in the present pack, i.e. there is no break between the packs. It is not very likely that the woman will have her menstrual bleeding until the end of the second pack, but she may experience spotting or break-through bleeding on the days she is taking tablets.
2. The woman may also be advised to stop taking tablets from the present pack. In that case she should keep a tablet-free period of up to 7 days, including those days when she forgot tablets, and then continue with the next pack.

In case the woman has forgotten tablets and then does not have her menstrual bleeding in the first normal tablet-free period, the possibility of pregnancy should be considered

<u>Advice in case of gastrointestinal disturbances</u>

In case of severe gastro-intestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.
If vomiting occurs within 3-4 hours after taking the active tablets, the advice concerning missed tablets, as given below, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to induce or postpone a withdrawal bleed
There is no indication for this product to postpone menstruation. However, in extraordinary cases, if postponing menstruation is required the woman should continue with another blister pack of Gedarel without a tablet-free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Gedarel is then resumed after the usual 7-day tablet-free interval.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

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

Method of administration

For oral administration.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the condition appear for the first time while taking oral contraceptives, the use of oral contraceptives should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE]).
  - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
  - Major surgery with prolonged immobilisation (see section 4.4).
  - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4).
- Presence or risk of arterial thromboembolism (ATE)
  - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris).
  - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA).
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
  - History of migraine with focal neurological symptoms (see section 4.4).
  - 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.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.

- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts)
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Gedarel is contraindicated for concomitant use with the 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 any of the conditions or risk factors mentioned below is present, the suitability of Gedarel 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 Gedarel should be discontinued.

Circulatory disorders

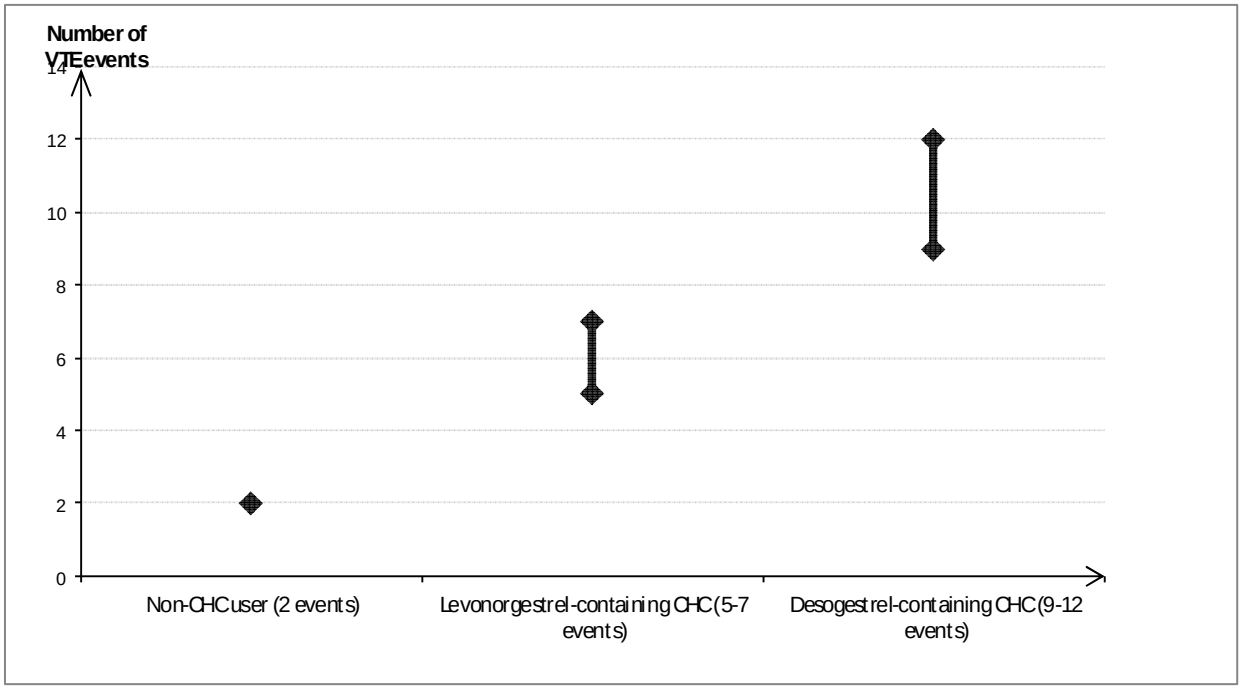
Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Gedarel may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Gedarel, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.**

In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).
It is estimated[1] that out of 10,000 women who use a CHC containing desogestrel between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.
In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.
VTE may be fatal in 1-2% of cases.

[1] These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs. [2] Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6.

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



Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

Gedarel 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 patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Gedarel has not been discontinued in advance.
Positive family history (venous	If a hereditary predisposition is suspected, the

thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	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). Gedarel 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.

Tumours

Epidemiological studies indicate that the long-term use of oral contraceptives displays an additional risk factor for the development of cervical cancer in women infected with human papillomavirus (HPV). However, there is still uncertainty about the extent to which this finding is influenced by confounding effects (e.g. differences in number of sexual partners or in use of barrier contraceptives).

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs). The increased risk gradually declines for 10 years after cessation of COC use. Since breast cancer is a rare condition in women below 40 years of age, the increase in the number of diagnosed cases of breast cancer in present and former users of COCs is low compared to the risk of breast cancer in their entire lifetime. These studies do not put forward evidence of a causal relationship. The observed pattern of an increased risk may be due to an earlier diagnosing of breast cancer in users of COCs, the biological effects of COCs or a combination of both. The diagnosed cases of breast cancer in users of COCs have a tendency to be less clinically advanced compared to the diagnosed cases of breast cancer in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of CHCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking CHCs.

Other conditions

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.

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

Women with hypertriglyceridaemia or a family history thereof, may be at an increased risk of pancreatitis when taking CHCs.

Although small increases in blood pressure have been reported in many women taking CHCs, clinically relevant increases are rare. A systemic relationship between CHC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a CHC then it is prudent for the physician to withdraw the CHC and treat the hypertension. Where considered appropriate, CHC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of a relationship with CHC use is inconclusive: Jaundice and/or itching in connection with cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss.

Acute or chronic disturbances of liver function may necessitate discontinuation of COC use until liver function parameters have been normalised. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although CHCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in well controlled diabetics using CHCs. However, diabetic women should be carefully observed while taking CHCs.

Crohn’s disease and ulcerative colitis have been reported during CHC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking CHCs.

Medical examination/consultation
Prior to the initiation or reinstitution of Gedarel 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 Gedarel 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 package leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.
Women should be advised that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy
The efficacy of Gedarel may be reduced in the event of e.g. missed tablets (section 4.2), gastro-intestinal disturbances (section 4.2) or concomitant medication that decrease the plasma concentration of ethinylestradiol and/or etonogestrel, the active metabolite of desogestrel (section 4.5).

Herbal preparations containing St. John's wort (Hypericum perforatum) should not be used while taking Gedarel due to the risk of decreased plasma concentrations and reduced clinical effects of Gedarel (see section 4.5).

Reduced cycle control
With all CHCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate, diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the CHC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before CHC use is continued.

<u>Excipient</u>
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

When counselling the choice of contraceptive method(s), all the above information should be taken into account.

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.

Pharmacodynamic interactions
During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3). Therefore, Gedarel users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. Gedarel can be restarted 2 weeks following completion of treatment with these combination drug regimens.

Pharmacokinetic interactions
Effects of other medicinal products on Gedarel
Interactions can occur with drugs that induce microsomal enzymes, **especially cytochrome P450 isoenzymes (CYP)**, which can result in increased clearance of sex hormones and lead to breakthrough bleeding and/or oral 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 enzyme-inducing active substances, another reliable, non-hormonal, method of contraception, which is not affected by enzyme-inducing medicinal products, 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.:
Phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, certain HIV protease inhibitors (e.g.ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz, nevirapine) and possibly also oxcarbazepine, topiramate, rifabutin, felbamate, griseofulvin, 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 (e.g. nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g. boceprevir, telaprevir) can increase or decrease plasma concentrations of 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.

Substances decreasing the clearance of Gedarel (enzyme inhibitors)
The clinical relevance of potential interactions with enzyme inhibitors remains unknown. Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel.

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 Gedarel on other medicinal products

Oral contraceptives may affect the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected.

Clinical data suggest that ethinylestradiol is inhibiting the clearance of CYPIA2 substrates leading to a weak (e.g. theopylylline) or moderate (e.g. tizanidine) increase in their plasma concentration.
Ciclosporin
Oral contraceptives may inhibit the metabolism of ciclosporin in the liver resulting in increased incidence of adverse events.

Lamotrigine
Combined oral contraceptives have been shown to induce the metabolism of lamotrigine which may result in subtherapeutic plasma levels of lamotrigine.

Tizanidine
Oral contraceptives may enhance the blood pressure lowering effect of titazinidine due to inhibition of the metabolism of tizanidine via CYP1A2.
Caution should be exercised when prescribing tizanidine to users of oral contraceptives due to the narrow therapeutic window of tizanidine.

Levothyroxine
Oestrogen therapy may lead to a reduction of free thyroxine and increase of TSH in hypothyroid women treated with levothyroxine.
The combination may be used with dose adjustment.

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, the plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters for carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Gedarel is not indicated in pregnancy.

If pregnancy occurs during treatment with Gedarel, further intake should be stopped. However, extensive epidemiological studies have neither showed an increased risk of birth defects in children born to women taking CHCs before pregnancy, nor any teratogenic effect when CHCs were taken inadvertently during early pregnancy.

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

Breastfeeding
Lactation may be influenced by CHCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of CHCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk, but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In the first part of the treatment period a large part (10-30%) of women may expect to get side effects such as breast tenderness, malaise and spot bleeding. However, these side effects are usually temporary and disappear after 2-4 months.

Description of selected adverse reactions
An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Other side effects have been reported in women using combined hormonal contraceptives. These are described in section 4.4.

As with all CHCs, changes in vaginal bleeding patterns may occur, especially during the first months of use. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration.

Possibly related undesirable effects that have been reported in users of Gedarel and users of combined hormonal contraceptives in general are listed in the table below[3]. All ADRs are listed by system organ class and frequency; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and not known (frequency cannot be estimated from the available data).

Systems Organ Class	***Very common*** **≥1/10**	***Common*** **≥1/100 to <1/10**	***Uncommon*** **≥1/1,000 to <1/100**	***Rare*** **≥1/10,000 to <1/1,000**	***Not known*** **(frequency cannot be estimated from the available data)**
Immune system disorders				Hypersensitivity reaction	Exacerbation of symptoms of hereditary and acquired angioedema
Metabolism and nutrition disorders			Fluid retention		
Psychiatric disorders		Depressed mood, Mood altered Nervousness	Libido decreased	Libido increased	
Nervous system disorders		Headache, Dizziness	Migraine		
Eye disorders				Contact lens intolerance	
Ear and labyrinth disorders			Otosclerosis		
Vascular disorders			Hypertension	Venous thromboembolism (VTE), Arterial thromboembolism (ATE)	
Gastrointestinal disorders		Nausea, Abdominal pain	Vomiting, Diarrhoea		
Skin and subcutaneous tissue disorders		Acne	Rash, Urticaria	Erythema nodosum, Erythema multiforme, Chloasma	
Reproductive system and breast disorders	Irregular bleeding	Breast pain, Breast tenderness, Amenorrhea, Dysmenorrhea, Premenstrual syndrome	Breast enlargement	Vaginal secretion Breast secretion	
Investigations		Weight increased		Weight decreased	

[3] The most appropriate MedDRA term to describe a certain adverse reaction is listed.

Synonyms or related conditions are not listed, but should be taken into account as well.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There have been no reports of serious, harmful effects after overdose.
Symptoms
Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding.

Treatment
There are no antidotes, and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Hormonal contraceptives for systemic use, Progestogens and estrogens, fixed combinations; ATC code: G03AA09

Mechanism of action
The contraceptive effect of CHCs is based on the interaction of different factors, out of which the most important is the inhibition of ovulation and the changes in the cervical secretion. Besides protection against pregnancy, CHCs have several positive properties which, next to the negative properties (see sections 4.4 and 4.8), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter.
The latter may result in a decrease in the occurrence of iron deficiency.
Also, it seems that the risk of endometrial cancer and ovarian cancer is reduced. Furthermore, it has been shown that high dosed combined hormonal contraceptives (50 microgram ethinylestradiol) reduce the risk of ovarian cysts, pelvic inflammatory disease, benign breast disorders, ectopic pregnancy and endometrial and ovarian cancer. Whether this also is the case for low dose combined hormonal contraceptives is not yet confirmed.

Paediatric population
No clinical data on efficacy and safety are available in adolescents below 18 years.

5.2 Pharmacokinetic properties

Desogestrel

Absorption
Orally administered desogestrel is rapidly and completely absorbed and converted to etonogestrel. Following ingestion of a single dose, peak serum concentrations of about 2 ng/mL are reached within 1.5 hours. Bioavailability is 62-81%.

Distribution
Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2-4% of the total serum drug concentrations are present as free steroid, 40-70% are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution of the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of desogestrel is 1.5 L/kg.

Biotransformation
Etonogestrel is completely metabolized by the known pathways of steroid metabolism. The metabolic clearance rate from serum is about 2 mL/min/kg. No interaction was found with the co-administered ethinylestradiol.

Elimination
Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted at a urinary to biliary ratio of about 6:4.

Steady-state conditions Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about two- to threefold, reaching steady state conditions during the second half of a treatment cycle.

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of a single dose, peak serum concentrations of about 45 pg/mL are reached within 1-2 hours. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%.

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

Biotransformation
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are

present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 mL/min/kg.
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 serum levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Unchanged drug is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions
Steady state concentrations are reached after 3-4 days when serum drug levels are higher by 30-40% as compared to single dose.

5.3 Preclinical safety data

Preclinical studies on ethinylestradiol and desogestrel revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.
However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Potato starch;
stearic acid;
all-rac-alpha-tocopherol;
lactose monohydrate;
magnesium stearate;
silica colloidal anhydrous;
povidone K 30;
quinoline yellow (E 104);

Tablet coating:
Hypromellose;
Macrogol 6000;
Propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30ºC. Store in the original package.

6.5 Nature and contents of container

PVC/PVDC-Aluminium blisters of 21 tablets per calendar blister strip available in packs containing 1×21, 3×21, 6×21 or 13×21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
1103 Budapest, Gyömrői út 19-21.
Hungary

8 MARKETING AUTHORISATION NUMBER(S)

PL 04854/0060

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/07/2013

10 DATE OF REVISION OF THE TEXT

05/01/2023