1. NAME OF THE MEDICINAL PRODUCT

Belara

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.030 mg ethinylestradiol and 2 mg chlormadinone acetate (equivalent to 1.71 mg chlormadinone).

Excipient with known effect: Each film-coated tablet contains 69.5 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pale pink, round, biconvex film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral hormonal contraceptive.

The decision to prescribe Belara should be made taking into consideration the individual woman's currently existing risk factors, particularly those relating to venous thromboembolism (VTE), and how the risk of VTE with Belara compares with other combined hormonal contraceptives (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology

One film-coated tablet must be taken every day at the same time (preferably in the evening) on 21 consecutive days, followed by a seven-day break in which no film-coated tablets are taken. Menstruation-like withdrawal bleeding should occur two to four days after administration of the last film-coated tablet. After the seven-day medication-free interval, medication should be continued with the next pack of Belara, regardless of whether bleeding has ceased or not.

The film-coated tablets should be pressed out of the blister pack at the position marked with the corresponding weekday and swallowed whole, if necessary, with a little liquid. The film-coated tablets are to be taken daily following the direction of the arrow.

Starting administration of the film-coated tablets

No previous administration of a hormonal contraceptive (during the last menstruation cycle)

The first film-coated tablet should be taken on day one of the women's natural cycle, i.e. on the first bleeding day of the next menstruation. If the first film-coated tablet is taken on the first day of menstruation, contraception starts on the first day of administration and also continues during the seven-day medication-free interval.

If menstruation had started more than five days earlier, then the woman should be instructed to wait until her next menstruation before starting to take Belara.

After a miscarriage or an abortion in the first trimester
After a miscarriage or an abortion in the first trimester administration of Belara can be started immediately. In this case no further contraceptive measures are necessary.

After childbirth or after a miscarriage or abortion after the third month of pregnancy
After childbirth women who do not breast-feed can start administration 21-28 days after delivery in which case no additional mechanical contraceptive measures are required.

If administration starts more than 28 days after childbirth, additional mechanical contraceptive measures are necessary during the first seven days.

If a woman has already had sexual intercourse, pregnancy must be ruled out or she must wait until her next menstruation before starting administration.

Lactation (see section 4.6).
Belara should not be taken by breast-feeding women.

After discontinuation of Belara
After discontinuation of Belara the current cycle may be prolonged by about a week.

Irregular tablet administration

If a user has forgotten to take a film-coated tablet, but takes it **within 12 hours** no further contraceptive measures are necessary. Users should continue taking the film-coated tablets as usual.

If the usual intake interval is **exceeded by more than 12 hours**, contraceptive protection may be reduced..
The last forgotten film-coated tablet should be taken immediately. The other film-coated tablets should be taken as usual. In addition other mechanical contraceptive measures, e.g. condoms, are also to be used for the next seven days. Normal withdrawal bleeding will probably not occur until the second pack has been used; however, breakthrough bleeding or spotting may often occur during tablet administration. If withdrawal bleeding does not occur after taking the second pack, then a pregnancy test should be carried out.
What to do in the event of vomiting or diarrhoea
If vomiting occurs within 4 hours after administration of the tablets or severe diarrhoea develops, absorption may be incomplete and reliable contraception is no longer ensured. In this case the instructions in "Irregular tablet administration" (see above) should be followed. Belara administration should be continued.

How to postpone a withdrawal bleed
To delay a period the woman should continue with another blister pack of Belara 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 Belara 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
Belara is only indicated after menarche. The safety and efficacy of chlormadinone acetate and ethinylestradiol in adolescents below 16 years has not been established. No data are available.

Elderly
Belara is not indicated after menopause.

4.3 Contraindications

Combined hormonal contraceptives should not be used in women with any of the conditions below. Belara should be discontinued immediately if one of these conditions occurs during administration:

- uncontrolled diabetes mellitus;
- uncontrolled hypertension or significant increase of blood pressure (values are persistently over 140/90 mmHg);
- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism – currently existing VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE]).
  - Known hereditary or acquired predisposition to venous thromboembolism, such as APC-resistance, (including Factor V Leiden mutation), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
  - Major surgery entailing prolonged immobilization (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 to arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
- History of migraine with focal neurological symptoms
- A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- Hepatitis, jaundice, liver function disorders until liver function values have returned to normal.
- Generalised pruritus, cholestasis, in particular during a previous pregnancy or oestrogen therapy.
- Dubin-Johnson syndrome, Rotor syndrome, bile-flow disorders.
- A history of, or existing, liver tumour.
- Severe epigastric pain, enlargement of the liver, or symptoms of intra-abdominal haemorrhage (see section 4.8).
- First occurrence or recurrence of porphyria (all three forms, in particular acquired porphyria).
- Presence, or a history, of malignant hormone-sensitive tumours, e.g. of the breast or uterus.
- Severe disorders of lipid metabolism.
- Pancreatitis or history of such a condition, if associated with severe hypertriglyceridaemia.
- Symptoms of migraine, when it occurs for the first time, or more frequent occurrence of unusually severe headaches.
- Acute sensory disorders, e.g. visual or hearing disorders.
- Motor disorders (particularly paresis).
- Increase in frequency of epileptic seizures.
- Severe depression.
- Otosclerosis deteriorating during previous pregnancies.
- Unexplained amenorrhoea.
- Endometrial hyperplasia.
- Unexplained genital bleeding.

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

One or more serious risk factors for venous or arterial thrombosis may be a contraindication (see section 4.4).

Concomitant use of Belara with medicines containing ombitasvir/paritaprevir/ritonavir and dazabuvir or glecaprevir/pibrentasvir is contraindicated (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Warnings

Smoking increases the risk of severe cardiovascular side-effects of combination oral contraceptives (COC). This risk increases with increasing age and cigarette consumption and is very pronounced in women above the age of 35 years. Smokers over the age of 35 years should use other contraceptive methods.

Combined hormonal contraceptives administration is associated with an increased risk of various serious diseases such as myocardial infarction, thrombo-embolism, stroke, or hepatic neoplasms. Other risk factors such as hypertension, hyperlipidaemia, obesity and diabetes distinctly increase the morbidity and mortality risk.

If any of the conditions or risk factors mentioned below is present, the suitability of Belara should be discussed with the patient.

If any of these conditions or risk factors are aggravated or emerge for the first time, the woman should be advised to seek the advice of her treating doctor, who will subsequently decide whether the use of Belara should be discontinued.

Thromboembolism and other vascular diseases
Epidemiological studies have shown an association between hormonal contraceptive use and an increased risk of venous or arterial thromboembolic diseases such as myocardial infarction, apoplexy, deep vein thrombosis and pulmonary embolism. These events are uncommon. Extremely rarely, thrombosis has been reported to occur in combined hormonal contraceptive users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk of Venous thromboembolism (VTE)
The use of any combined hormonal contraceptive entails a higher risk of venous thromboembolism (VTE) than if the product is not used. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. It is not yet known how the risk with Belara compares with the risk with levonorgestrel-containing products. The decision to use any product other than one known to have the lowest VTE risk should be taken only after a discussion with the patient, thereby ensuring that she has understood the risk of VTE associated with Belara, and furthermore how her existing risk factors affect this risk, and that she is aware that the risk of VTE risk is at its highest in the first ever year of use. There is also some evidence that the risk is increased when the use of a combined hormonal contraceptive is resumed following a respite in its use for 4 weeks or more.

In women who do not use a combined hormonal contraceptive and are not pregnant, about 2 out of 10,000 will develop a VTE during a one-year period. 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 hormonal contraceptives (CHC) (<50pg ethinylestradiol) have found that out of 10,000 women about 6 to 12 will develop a VTE in one year.

Out of 10,000 women who use a levonorgestrel-containing CHC about 6[1] will develop a VTE in one year.

It is not yet know how the risk with chlormadinone-containing CHCs compares with the risk with levonorgestrel-containing CHCs.

This annual number of VTEs is lower than the number expected during pregnancy or in the postpartum period. The VTE may have a fatal outcome in 1-2% of cases.

Risk factors for VTE
The risk for venous thromboembolic complications in combined hormonal contraceptive users may increase substantially in a woman with additional risk factors, particularly if several of the risk factors are present (see table).
Belara is contraindicated if a woman has multiple risk factors that put her at high risk of developing 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 taken into consideration. If the balance of benefits and risks is considered to be negative a combined hormonal contraceptive should not be prescribed (see section 4.3).

[1] ~~Mid-point of range of 5-7 per 10,000 WY, based on~~ a relative risk for combined hormonal contraceptives containing levonorgestrel, versus the approximately 2.3-3.6 range observed without the use of such products.

Table: Risk factors for VTE

Risk factor	*Notes*
Obesity (body mass index greater than 30 kg/m^2)	Risk increases significantly with an increase in the BMI. It is particularly important to take this into consideration if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the lower limbs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation, including air travel of >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 (at least 4 weeks prior to elective surgery) and to only resume its use after two weeks have elapsed following full remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic therapy should be considered if the use of Belara has not been discontinued in advance.
Positive family history (venous thromboembolism at any time in a sibling or parent, especially if it developed at a relatively early age, e.g. before 50).	If a hereditary predisposition is suspected, advice should be sought from a specialist before any decision is made with regard to the use of a combined hormonal contraceptive.
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 anaemia
Advanced 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 puerperium period, 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 they are taking a combined hormonal contraceptive.

Symptoms of deep vein thrombosis (DVT) can include:
- swelling of the lower leg and/or foot on one side or along a vein in the leg;
- pain or tenderness in the leg, which may be felt by the patient 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 may be confused with more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include sudden pain, swelling and the slight blueish discoloration of an extremity.

If the occlusion occurs in the eye, symptoms can range from a painless blurring of vision to progressive loss of vision. Sometimes the loss of vision occurs almost immediately.

Risk of arterial thromboembolism (ATE)
Epidemiological studies have associated the use of combined hormonal contraceptives with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events can be fatal.

Risk factors for ATE
The risk of arterial thromboembolic complications (myocardial infarction) or of a cerebrovascular accident in combined hormonal contraceptive users increases in women with risk factors (see table). Belara is contraindicated if a woman has one serious risk factor, or multiple risk factors, that put her at a 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 taken into consideration. If the balance of benefits and risks is considered to be negative a combined hormonal contraceptive should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	*Notes*
Advanced age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a combined hormonal contraceptive. 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/m2)	Risk increases substantially as BMI increases. This is especially important in women with additional risk factors.
Positive family history (arterial thromboembolism at any time in a sibling or parent, especially if it developed at a relatively early age, e.g. before 50).	If a hereditary predisposition is suspected, advice should be sought from a specialist before any decision is made with regard to the use of a combined hormonal contraceptive.
Migraine	The frequency or severity of migraine may increase during combined hormonal contraceptive use (which may be the precursor of a cerebrovascular event), and therefore it my be a reason for immediately discontinuing the use of the product.
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 they are taking a combined hormonal contraceptive.

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 difficulty walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding speech;
- sudden difficulty seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting, with or without a seizure.

Temporary symptoms suggest that 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 fullness or indigestion, or a feeling of suffocation;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeat;

Women who are taking combined hormonal contraceptives should be informed that they should consult their doctor if they develop possible symptoms of thrombosis. Belara should be stopped if thrombosis is suspected or confirmed.

Tumours

Some epidemiological studies indicate that the long-term use of hormonal contraceptives is a risk factor for the development of cervical cancer in women infected with the human papilloma virus (HPV). However, there is still controversy about the extent to which this finding is influenced by confounding effects (e.g. differences in the number of sexual partners or the use of mechanical contraceptive measures) (see also "Medical examination").

A meta-analysis from 54 epidemiological studies reported a slightly increased risk (RR = 1.24) of breast cancer in women who are currently using CHCs. This increased risk is transient and during the course of 10 years after cessation of CHC use this risk gradually decreases. These studies do not suggest evidence for causation. It is possible that this increased risk observed may be due to factors such as: early diagnosis of breast cancer in women taking combined hormonal contraceptives, the biological effects of combined hormonal contraceptives, or a combination of the two factors.

In rare cases benign, and in even fewer cases malignant, liver tumours have been reported during the administration of oral contraceptives. In isolated cases these tumours have led to life-threatening intra-abdominal haemorrhage. In the event of severe abdominal pain that does not recede spontaneously, hepatomegaly or signs of intra-abdominal haemorrhage the possibility of a liver tumour must be taken into account and Belara must be discontinued.

Other conditions

Depressed mood and depression are well-known adverse effects of hormonal contraceptive use (see section 4.8). Depression can be severe and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their doctor if they experience mood changes or depressive symptoms, even immediately after starting treatment.

Many women taking hormonal contraceptives had a slight increase in blood pressure; however a clinically significant increase is rare. The connection between the administration of hormonal contraceptives and clinically manifest hypertension has not been confirmed. If there is a clinically significant increase in blood pressure during the administration of Belara, the preparation should be discontinued and the hypertension treated. Belara can be continued as soon as blood pressure values have returned to normal on antihypertensive therapy.

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

In women with a history of herpes gestationis there may be a herpes recurrence during CHC administration.

In women with a history of hypertriglyceridaemia or a family history of such the risk of pancreatitis is increased during CHC administration. Acute or chronic disturbances of liver function may necessitate discontinuation of CHC use until the liver function values return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex hormones necessitates discontinuation of CHCs.

CHCs may affect peripheral insulin resistance or glucose tolerance. Therefore diabetics should be monitored carefully whilst taking oral contraceptives.

Uncommonly, chloasma may occur, particularly in women with a history of chloasma gravidarum. Women with a tendency to develop chloasma should avoid exposure to the sun and ultraviolet radiation during the administration of hormonal contraceptives.

Precautions

The administration of oestrogen or oestrogen/progestogen combinations may have negative effects on certain diseases/conditions. Special medical supervision is also necessary

- epilepsy
- multiple sclerosis
- tetany
- migraine (see section 4.3)
- asthma
- cardiac or renal insufficiency
- chorea minor
- diabetes mellitus (see section 4.3)
- liver diseases (see section 4.3)
- dyslipoproteinaemia (see section 4.3)
- auto-immune diseases (including systemic lupus erythematosus)
- obesity
- hypertension (see section 4.3)
- endometriosis
- varicosity
- phlebitis (see section 4.3)
- coagulation disorders (see section 4.3)
- mastopathy
- myoma uteri
- herpes gestationis
- depression
- chronic inflammatory bowel diseases (Crohn’s disease, ulcerative colitis; see section 4.8)

Medical examination/consultation

Prior to starting or resuming the use of Belara, 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 risks of Belara as compared with those of other combined hormonal contraceptives, 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 patient information leaflet and follow the advice given. The frequency and nature of examinations should be based on established practice guidelines, and should be performed in a manner that is adapted to the individual woman.
Women should be advised that hormonal contraceptives do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Impaired efficacy
Omission of a film-coated tablet (see "Irregular tablet administration"), vomiting or intestinal disorders including diarrhoea, the long-term concomitant administration of certain medicinal products (see section 4.5) or in very rare cases metabolic disorders may impair contraceptive efficacy.

Impact on cycle control

Breakthrough bleeding and spotting
All oral contraceptives may cause irregular vaginal bleeding (breakthrough bleeding/spotting) particularly in the first few administration cycles. Therefore a medical assessment of irregular cycles should only be made after an adjustment period of about three cycles. If during administration of Belara breakthrough bleeding persists or occurs after previously regular cycles, an examination should be carried out to rule out pregnancy or an organic disorder. After pregnancy and an organic disorder have been ruled out, Belara can be continued or a switch made to another preparation.

Intracyclic bleeding may be a sign of impaired contraceptive efficacy (see "Irregular tablet administration", "Instructions in case of vomiting" and section 4.5).

Absence of withdrawal bleeding
After 21 days of administration withdrawal bleeding usually occurs. Occasionally and particularly in the first few months of administration withdrawal bleeding may be absent. However, this need not to be an indication of a reduced contraceptive effect. If bleeding is not present after one administration cycle in which a film-coated tablet was not forgotten, the tablet-free period of seven days was not extended, no other medicines were taken concomitantly, and there was no vomiting or diarrhoea, conception is unlikely and the administration of Belara can be continued. If Belara was not taken according to instructions before the first absence of withdrawal bleeding or withdrawal bleeding does not occur in two consecutive cycles, pregnancy must be ruled out before continuing administration.

Herbal medicines containing St-John's-wort (*Hypericum perforatum*) should not be taken together with Belara (see section 4.5).

Elevated ALAT levels
In clinical trials, in hepatitis C-infected patients treated with ombitasvir/paritaprevir/ritonavir and dazabuvir (with or without ribavirin), an increase in ALAT levels of more than five times the upper limit of normal level was significantly more frequent in women taking ethinylestradiol-containing drugs, such as combined hormonal contraceptives. In addition, in patients treated with glecaprevir/pibrentasvir, an increase in ALAT levels was also observed in women taking ethinylestradiol-containing medicines such as combined hormonal contraceptives (see sections 4.3 and 4.5).

Excipient
This medicine contains 69.5 mg of lactose monohydrate per tablet. This product should not be used in patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption.

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
Concomitant use with ombitasvir/paritaprevir/ritonavir and dazabuvir (with or without ribavirin) or glecaprevir/pibrentasvir may increase the risk of elevated ALAT levels (see sections 4.3 and 4.4). Therefore, women taking Belara should switch to

a different method of contraception (e.g. a progestogen-only contraceptive or a non-hormonal method) before starting treatment with the combination. Belara can be started again two weeks after the end of treatment.

Pharmacokinetic interactions

Effects of other medicines on Belara film-coated tablets

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.

Treatment
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 ingredients, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature:

Active ingredients increasing the clearance of COCs (diminished efficacy of COCs due to enzyme-induction), e.g.:

Barbiturates, bosentan, carbamazepine, barbexaclone, phenytoin, primidone, modafinil, rifampicin, rifabutin, 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*).

The following medicines/agents may reduce serum concentrations of ethinylestradiol:
- any medicine that increases gastrointestinal motility (e.g. metoclopramide) or reduces absorption (e.g. activated charcoal).

Active ingredients 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 oestrogen 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 reviewed 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.

The following medicines/agents may increase serum concentrations of ethinylestradiol:

- active ingredients that inhibit the sulphation of ethinylestradiol in the intestinal wall, such as ascorbic acid or paracetamol;
- atorvastatin (increases ethinylestradiol AUC by 20%);
- drugs that inhibit liver microsomal enzymes, such as imidazole-type antifungals (e.g. fluconazole), indinavir or troleandomycin.

Effects of Belara film-coated tablets on other medicinal products

- Inhibition of hepatic microsomal enzymes and consequent increase in serum concentrations of certain drugs such as diazepam (and other benzodiazepines metabolized by hydroxylation), cyclosporine, theophylline and prednisolone;
- Induction of glucuronidation in the liver and consequent reduction of serum concentrations of certain drugs such as lamotrigine, clofibrate, paracetamol, morphine and lorazepam.

Because of the effects on glucose tolerance, the insulin requirement or the dose of oral antidiabetics required may be modified (see section 4.4).

This may also apply to medicines you have taken recently.

The prescribing information of such medicines should be reviewed to see if there are any possible interactions with Belara.

Laboratory tests
The use of contraceptive steroids may influence the results of certain laboratory tests (such as liver, thyroid, adrenal and renal function tests), blood levels of (carrier) proteins (e.g. corticosteroid-binding globulins), and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Belara is not indicated during pregnancy. Prior to using the medicine pregnancy must be ruled out. If pregnancy occurs during Belara treatment, the medicinal product is to be discontinued immediately. Extensive epidemiological studies have shown no clinical evidence of teratogenic or foetotoxic effects when oestrogens were accidentally taken during pregnancy in combination with other progestogens in doses similar to those in Belara. Although animal experiments have shown evidence of reproduction toxicity (see section 5.3), clinical data of more than 330 exposed human pregnancies did not show any embryotoxic effects of chlormadinone acetate.

The heightened risk of VTE in the postpartum period should be considered when resuming Belara (see sections 4.2 and 4.4).

Lactation
Lactation may be affected by oestrogens as they may affect the quantity and composition of the breast milk. Small quantities of contraceptive steroids and/or their metabolites may be excreted in the breast milk and may affect the breast-fed infant. Therefore, Belara should not be used during lactation.

4.7 Effects on ability to drive and use machines

Combined hormonal contraceptives are not known to have negative effects on the ability to drive or to operate machines.

4.8 Undesirable effects

Clinical studies with Belara have shown that the most common side- effects (> 20%) were breakthrough bleeding, spotting, headache and breast discomfort. Irregular bleeding usually decreases with continuation of the intake of Belara.

The following side-effects have been reported after administration of Belara in a clinical study with 1,629 women.

Frequency of undesirable effects / *Organ system (MedDRA)*	**Very common (≥1/10)**	**Common (≥1/100 - <1/10)**	**Uncommon (≥1/1000 - <1/100)**	**Rare (≥1 / 10,000 - <1 / 1,000)**	**Very rare (<1/10,000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations			vaginal candidiasis	vulvovaginitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)			fibroadenoma of the breast			
Immune system disorders			drug hypersensitivity, including allergic skin reactions			exacerbation of symptoms of hereditary and acquired angioedema
Metabolism and nutrition disorders			changes in blood lipid levels, including hypertriglyceridaemia	increased appetite		
Psychiatric disorders		depressed mood, nervousness, irritability	reduced libido			
Nervous system disorders		dizziness, migraine (and/or aggravation of migraine)				
Eye disorders		visual disturbance		conjunctivitis, contact lens intolerance		
Ear and labyrinth disorders				sudden hearing loss, tinnitus		

Frequency of undesirable effects / *Organ system (MedDRA)*	**Very common (≥1/10)**	**Common (≥1/100 - <1/10)**	**Uncommon (≥1/1000 - <1/100)**	**Rare (≥ 1 / 10,000 - <1 / 1,000)**	**Very rare (<1/10,000)**
Vascular disorders				hypertension, hypotension, cardiovascular collapse, varicose vein, venous thrombosis, venous/arterial thromboembolism (VTE/ATE)*	
Gastrointestinal disorders	feeling sick (nausea)	vomiting	abdominal pain, abdominal distension,		
Skin and subcutaneous tissue disorders		acne	pigmentation disorder, chloasma, alopecia, dry skin, increased sweating, hair loss	urticaria, eczema, erythema, pruritus, aggravated psoriasis, hypertrichosis	erythema nodosum
Musculoskeletal and connective tissue disorders		sensation of heaviness	back pain, muscle disorders		
Reproductive system and breast disorders	vaginal discharge, dysmenorrhoea, amenorrhoea	lower abdominal pain	galactorrhoea,	breast enlargement, vulvovaginitis, menorrhagia, premenstrual	
General disorders and administration site conditions		fatigue, oedema, increased weight			
Investigations		elevated blood pressure			

*See Description of selected adverse reactions

In addition, the following adverse reactions have been reported in the post-marketing period with ethinylestradiol and chlormadinone acetate: weakness and other allergic skin reactions not related to immune system diseases.

Description of selected adverse reactions

The following side-effects have also been reported on administration of combined hormonal contraceptives including 0.030 mg ethinylestradiol and 2 mg chlormadinone acetate:

- 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 combined hormonal contraceptives. These are discussed in more detail in section 4.4.
- An increased risk of biliary tract diseases has been reported in some studies on the long-term administration of CHCs.
- In rare cases benign, and even more rarely, malignant liver tumours have been observed after the administration of hormonal contraceptives, and in isolated cases have resulted in life-threatening intra-abdominal haemorrhage (see section 4.4).
- Aggravation of chronic inflammatory bowel disease (Crohn´s disease, ulcerative colitis; see section 4.4).

For other serious side-effects such as cancer of the cervix or breast see section 4.4.

Interactions
Breakthrough bleeding and/or contraceptive failure can occur because of interactions with other drugs (causing enzyme-induction) (see section 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important, because it allows continued monitoring of the benefit/risk profile of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/.

4.9 Overdose

There is no information on serious toxic effects in the case of an overdose. The following symptoms may occur nausea, vomiting and, particularly in young girls, slight vaginal bleeding. There is no antidote, symptomatic treatment should be applied. Monitoring of the electrolyte and water balance and liver function may be necessary in rare cases.

5. PHARMACOLOGY: PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, progestogens and oestrogens, fixed combinations. ATC code: G03AA15

Mechanism of action
The continuous intake of Belara for 21 days inhibits pituitary FSH and LH secretion, and thus ovulation. The endometrium proliferates and undergoes secretory transformation. The consistence of the cervical mucus is changed. This prevents sperm migration through the cervical canal and alters sperm motility.

The lowest daily dose of chlormadinone acetate for complete inhibition of ovulation is 1.7 mg. The full endometrial transformation dose is 25 mg per cycle.

Chlormadinone acetate is an antiandrogenic progestogen. Its effect is based on its ability to displace androgens from their receptors.

Clinical efficiency
In clinical studies in which the administration of film-coated tablets contain 0.03 mg ethinylestradiol and 2 mg chlormadinone acetate was tested for up to 2 years in 1,655 women and more than 22,000 menstruation cycles, there were 12 pregnancies. In 7 women the following factors were present during

the period of conception: drug administration errors, concomitant diseases causing nausea or vomiting,

or concomitant administration of medicines known to reduce the contraceptive effect of hormonal contraceptives.

Method of use	Number of pregnancies	Pearl index	95% confidence interval
Typical use	12	0.698	[0.389; 1.183]
Perfect use	5	0.291	[0.115; 0.650]

5.2 Pharmacokinetic properties

Chlormadinone acetate (CMA)

Absorption
On oral administration CMA is rapidly and almost completely absorbed. The systemic bioavailability of CMA is high as it is not subject to first-pass metabolism. Peak plasma concentrations are reached after 1-2 hours.

Distribution
The binding of CMA to human plasma proteins, mainly albumin, is more than 95%. CMA has no binding affinity for SHBG or CBG. CMA is stored primarily in fatty tissue.

Biotransformation
Various reduction and oxidation processes and conjugation to glucuronides and sulphates result in a variety of metabolites. The principal metabolites in human plasma are 3α- and 3ß-hydroxy-CMA with biological half-lives that do not differ essentially from that of non-metabolised CMA. The 3-hydroxy metabolites show similar antiandrogenic activity as CMA itself. In the urine the metabolites appear mainly as conjugates. After enzymatic cleavage the main metabolite is 2α-hydroxy-CMA besides the 3-hydroxy-metabolites and dihydroxy metabolites.

Elimination
CMA is eliminated from the plasma with a mean half-life of about 34 hours (after a single dose) and about 36-39 hours (after multiple doses). After oral administration CMA and its metabolites are excreted both renally and in the faeces in about equal amounts.

Ethinylestradiol (EE)

Absorption
EE is rapidly and almost completely absorbed after oral administration and mean peak plasma concentrations are reached after 1.5 hours. Due to presystemic conjugation and first-pass metabolism in the liver the absolute bioavailability is only about 40% and is subject to considerable interindividual variation (20-65%).

Distribution
The EE plasma concentrations reported in the literature vary considerably. Approximately 98% of the EE is bound to plasma proteins, almost exclusively to albumin.

Biotransformation
Like natural oestrogens, EE is biotransformed via (cytochrome P-450 mediated) hydroxylation at the aromatic ring. The main metabolite is 2-hydroxy-EE, which is metabolised to other metabolites and conjugates. EE undergoes presystemic conjugation both in the mucosa of the small intestine and the liver. Mainly glucuronides are found in the urine, while mainly sulphates are found in the bile and plasma.

Elimination
The mean plasma half-life of EE is approximately 12-14 hours. EE is excreted via the kidneys and faeces in a ratio of 2:3. The EE sulphate excreted in the bile after hydrolysis by intestinal bacteria passes into the enterohepatic circulation.

5.3 Preclinical safety data

The acute toxicity of oestrogens is low. Due to the pronounced differences between experimental animal species and in relation to humans, the results of animal studies with oestrogens have only limited predictive value for humans. Ethinylestradiol, a synthetic oestrogen frequently used in oral contraceptives, has an embryolethal effect in laboratory animals even in relatively low doses; anomalies of the urogenital tract and feminisation of male foetuses have been observed. These effects are regarded as species-specific.

Chlormadinone acetate has exhibited embryolethal effects in rabbits, rats and mice. Moreover, teratogenicity was observed at embryotoxic doses in rabbits and already at the lowest dose tested (1 mg/kg/day) in mice. The significance of these findings for human administration is unclear.

Preclinical data from conventional studies on chronic toxicity, genotoxicity and carcinogenic potential showed no special risks for humans apart from those already described in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate,
maize starch,
povidone K30,
magnesium stearate.

Tablet film coating:
hypromellose
lactose monohydrate,
macrogol,
propylene glycol,
talc,
titanium dioxide (E 171),
red iron oxide (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

6.4 The expiry date of the product is indicated on the packaging materials. Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

1x21 or 3x21 film-coated tablets in PVC/PVDC//Al blisters and in a box

6.6 Special precautions for disposal and other handling

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

Medicinal product subject to medical prescription

7. Manufacturer

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

8. Registration Holder

TEC-O-PHARM-LIBRA LTD

POB 290, MODIIN 7171102

9. MARKETING AUTHORISATION NUMBER(S)

127-34-30410-0

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