BELARA

SUMMARY OF PRODUCT CHARACTERISTICS

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.

The use of combined hormonal contraceptives (CHCs) is associated with an increased risk of venous and arterial thromboembolism, particularly during the first year of use and when reinitiating after an interruption of 4 weeks or longer (see section 4.4)

Assess and discuss with the patient individual risk factor for thromboembolism before prescribing CHCs. Educate patient on signs and symptoms of thrombosis and the importance of prompt medical attention if these occur. (see section 4.4)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral hormonal contraceptive.

The decision to prescribe Belara should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Belara compares with other combined hormonal contraceptives (CHCs)(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) for 21 consecutive days, followed by a seven-day break during which no film-coated tablets are taken, menstruation-like withdrawal bleeding should occur two to four days after taking 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 the bleeding has stopped or not.

The film-coated tablet should be pressed out of the blister strip at the position marked with the

corresponding day of the week and swallowed in whole, with some liquid as needed. The film-coated tablets are to be taken daily, following the direction of the arrow.

Starting the administration of the film-coated tablets

No preceding hormonal contraceptive use (during the last menstruation cycle)

The first film-coated tablet has to be taken on day one of the women's natural cycle, i.e. on the first day of the next menstrual bleeding.. If the first film-coated tablet is taken on the first day of the menstruation, contraception starts on the first day of administration and also continues during the seven-day medication-free interval .If the menstruation had started more than five days earlier, then it should be pointed out that starting to take Belara will have to be delayed until the next menstruation.

Following a first-trimester miscarriage or abortion
After a miscarriage or an abortion in the first trimester, the use of Belara may be started immediately, and, in this case no further contraceptive measures are necessary.

Following Delivery, miscarriage or after the third month of pregnancy
Women who do not breast-feed may start administration 21-28 days after delivery, and in this case no additional mechanical contraceptive measures are required.

If the tablet-taking starts more than 28 days after delivery, additional mechanical contraceptive measures are necessary during the first seven days.

However, if intercourse has already occurred, pregnancy must be ruled out or the woman 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 delayed by about a week.

Irregular tablet administration

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

If the user is more than 12 hours late in taking the film-coated tablet, contraceptive protection may be reduced.

The last forgotten film-coated tablet should be taken immediately. The following film-coated tablets should be taken as usual. Additionally, 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 taking. If withdrawal bleeding does not occur after conclusion of the second pack, then a pregnancy test should be carried out.

Instructions in case of vomiting or diarrhoea

If vomiting occurs within 4 hours after taking the tablet or severe diarrhoea develops, absorption may be incomplete and reliable contraception is no longer ensured. In this case, instructions in section "Irregular tablet administration" (see above) should be followed. The use of Belara 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 may be continued for as long as preferred, until taking the last pill of the second pack. During the extension breakthrough-bleeding or spotting may be experienced. Following the usual 7-day tablet-free period, regular use of Belara may be resumed..

In order to shift the menstruation to another day of the week different from the one occurring according to current regimen, shortening of the next tablet-free interval is advised, by as many days as she preferred. The shorter the interval, the higher the risk of not having a withdrawal bleed, and the occurrence of breakthrough bleeding and spotting during the subsequent pack (just as when delaying the 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 the following conditions . Belara should be discontinued immediately if one of these conditions occurs during administration:

Uncontrolled diabetes mellitus;

Uncontrolled hypertension or a significant increase in blood pressure (values constantly above 140/90 mmHg).

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 mutation), antithrombin-III-deficiency, protein-C deficiency, protein-S deficiency.

Major surgery with prolonged immobilisation (see section 4.4).

A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4).

Presence or risk of arterial thromboembolism (ATE)

Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris).

Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
History of migraine with focal neurological symptoms.
A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
diabetes mellitus with vascular symptoms
severe hypertension
severe dyslipoproteinaemia
Hepatitis, jaundice, liver function disorders until liver function values have returned to normal.
Generalised pruritus, cholestasis, in particular during a previous pregnancy or estrogen therapy.
Dubin-Johnson syndrome, Rotor syndrome, bile-flow disorders.
Meningioma or history of meningioma.
A history of, or existing, liver tumours.
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.
Presence or history of Pancreatitis, if associated with severe hypertriglyceridemia.
First time occurrence of symptoms of migrainous headache, or more frequent occurrence of unusually severe headache.
Acute sensory disorders, e.g. visual or hearing disorders.
Motor disorders (particularly paresis).
Increase of the frequency of epileptic seizures.
Severe depression.
Otosclerosis deteriorating during previous pregnancies.
Inexplicable amenorrhoea.
Endometrial hyperplasia.
Unexplained genital bleeding.

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

One severe risk factor or risk factors for venous or arterial thrombosis may constitute a contraindication (see section 4.4).

Belara 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
Smoking increases the risk of severe cardiovascular side effects of the combined hormonal contraceptive (CHC). This risk increases with increasing age and cigarette consumption, and is very pronounced in women above the age of 35 years. Women above the age of 35 who smoke should use other contraceptive methods.

The use of CHCsis associated with an increased risk of various serious diseases such as myocardial infarction, thromboembolism, stroke, or hepatic neoplasms. Other risk factors such as hypertension, hyperlipidaemia, obesity and diabetes distinctly increase the risk of morbidity and mortality.

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

Thromboembolism and other vascular diseases
Results from epidemiological studies show that there is a connection between the administration of hormonal contraceptives and an increased risk of venous or arterial thromboembolic diseases, e.g. myocardial infarction, apoplexy, deep-vein thrombosis and pulmonary embolism. These events are rare. 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 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 CHCs containing Chlormadinone/Ethinylestradiol such as Belara may have a 1.25-fold increased risk compared to LNG. 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 woman to ensure she understands the risk of VTE with Belara, 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).

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

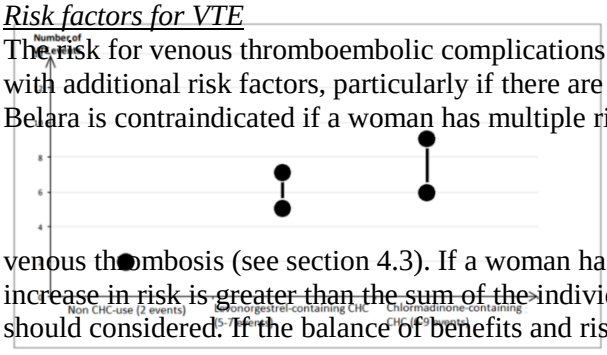
It is estimated that out of 10,000 women who use a CHC containing chlormadinone between 6 and 9 womenwill develop a VTE in one year.

This compares with about 6[1] in women who use a levonorgestrel-containing CHC.

The number of VTE events per 10,000 women in one year

The number of VTEs per year with low dose CHCs is fewer than the numbers expected in women during pregnancy or in the postpartum period. VTE may be fatal in 1-2% of cases.

Risk factors for VTE
The risk for venous thromboembolic complications in CHC users may increase substantially in women with additional risk factors, particularly if there are multiple risk factors (see table).
Belara 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 considered. If the balance of benefits and risks is considered to be negative 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)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors are 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 Belara has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent, especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any 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 anaemia
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 lightheadedness 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 CHC with an increased risk for arterial thromboembolism 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 (myocardial infarction) or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Belara 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/m2)	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. bellow 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHCuse.
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;

CHC users must be informed that they must consult their physician in the event of presenting possible symptoms of thrombosis. Belara must be discontinued upon suspicion or confirmation of thrombosis.

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 interfering factors (e.g. differences in the number of sexual partners or the use of mechanical contraceptive measures) (see also section "Medical examination").

A meta-analysis of 54 epidemiological studies reported a slight increase of relative risk (RR = 1.24) of having breast cancer diagnosed in users of CHCs. The excess risk is transient, and disappears gradually during the course of the 10 years after cessation of CHC use. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in CHC users, the biological effects of CHCs or a combination of both.

In rare cases benign, and in even fewer cases malignant, liver tumours have been reported during the administration of hormonal 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 considered and Belara must be discontinued.

Meningioma:

The occurrence of meningiomas (single and multiple) has been reported in association with use of chlormadinone acetate, especially at high doses and for prolonged time (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any chlormadinone acetate-containing treatment, must be stopped, as a precautionary measure.

There is some evidence that the meningioma risk may decrease after treatment discontinuation of chlormadinone acetate.

Other diseases

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.

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 so far not been confirmed. If there is a clinically significant increase in blood pressure during the administration of Belara, the use of the medicinal product must be discontinued and the hypertension must be treated. Belara may 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 recurrence during CHC administration.

In women with a history or familial history of hypertriglyceridaemia, 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 that occurred first during pregnancy or during 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 hormonal 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 estrogen or estrogen/progestogen combinations may have negative effects on certain diseases and/or conditions. Special medical supervision is necessary in:

- 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 ,
- varicosis,
- phlebitis (see section 4.3),
- blood coagulation disorders (see section 4.3),
- mastopathy,
- uterine myoma,
- herpes gestationis,
- depression,
- chronic inflammatory bowel diseases (Crohn’s disease, ulcerative colitis; see section 4.8)

Medical examination/consultation
Prior to the initiation or reinstitution 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 risk of Belara compared with other CHCs, the symptoms of VTE and ATE, the known risk factors, and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere 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 infection (AIDS) and other sexually transmitted diseases.

Impaired efficacy
Failing to take a film-coated tablet (see section "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.

The effect of the medicinal product on cycle control

Breakthrough bleeding and spotting
All hormonal contraceptives may cause irregular vaginal bleeding (breakthrough bleeding or 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 organ disorder. After pregnancy and an organ disorder have been ruled out, Belara can be continued, or a switch may be made to another medicinal product.

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

Absence of withdrawal bleeding
After 21 days of administration withdrawal bleeding usually occurs. Occasionally, particularly in the first few months of administration, withdrawal bleeding may be absent. However, this absence is not an indication of a reduced contraceptive effect. If bleeding is not present after one administration cycle during 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 may be continued. If Belara was not taken according to the 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).

Excipient
This medicinal product contains 69.5 mg lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Pharmacokinetic interactions

Effects of other medicinal products on Belara film-coated tablet

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 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 is recommended.

The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:

Barbiturates, bosentan, carbamazepine, 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 medicinal products/active substances may reduce the serum concentrations of ethinylestradiol:

- All medicines that increase gastrointestinal motility (e.g. metoclopramide) or impair absorption (e.g. activated charcoal);

Substances with variable effects on the clearance of COCs:

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

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

The following medicinal products/active substances may increase the serum concentration of ethinylestradiol:

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

Effects of Belara film-coated tablets on other medicinal products

- By inhibiting the hepatic microsomal enzymes thus consequently raising the serum concentration of active substances such as diazepam (and other benzodiazepines metabolised by hydroxylation), ciclosporine, theophylline and prednisolone;
- By inducing hepatic glucuronidation thus sonsequently reducing serum concentrations of e.g. lamotrigine, clofibrate, paracetamol, morphine and lorazepam.

Insulin or oral antidiabetic requirements may need to be altered due to effects on glucose tolerance (see section 4.4).

This may also apply to medicines taken recently.

The summary of product characteristics of the prescribed medicinal product should be checked for possible interactions with Belara.

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

4.6 Fertility, pregnancy and lactation

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

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

Breast-feeding
Lactation may be affected by estrogens as they may alter the quantity and the composition of the breast-milk. Small quantities of contraceptive steroids and/or their metabolites may be excreted in the breast-milk and may thus affect the child. 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 frequent side- effects (> 20%) were breakthrough bleeding, spotting, headache and breast pain. 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 / *System Organ Class (MedDRA)*	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1 / 10,000 to <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 (incl cysts and polyps)			fibroadenoma of 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 lipids including hyper-triglyceridaemia aemia	increased appetite		
Psychiatric disorders		depressed mood, nervousness, irritability	decreased libido			
Nervous system disorders		dizziness, migraine (and/or aggravation of migraine)				
Eye disorders		visual disturbance		conjunctivitis, contact lens intolerance		
Ear and labyrinth disorders				sudden hear 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 section, Description of selected adverse reactions

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

Description of selected adverse reactions

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

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

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) (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; treatment is symptomatic. 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 estrogens, 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 consistency 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 required dose for full endometrial transformation 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 efficacy
In clinical studies where the administration of a film-coated tablet containing 0.03 mg ethinylestradiol and 2 mg chlormadinone acetate was studied for up to a maximum of 2 years in 1,655 women and throughout more than 22,000 menstruation cycles, 12 pregnancies occurred. In case of 7 women, the

following factors were present during the period of conception: administration errors, concurrent diseases causing nausea or vomiting, or concurrent use of medicines that were known to reduce the contraceptive effect of hormonal contraceptives.

Type 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
After 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 the adipose tissue.

Biotransformation
Various reduction and oxidation processes and conjugation to glucuronides and sulphates result in various metabolites. The principal metabolites in human plasma are the 3α- and 3ß-hydroxy-CMA with biological half-lives not differing substantially 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- 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 via the kidneys 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. Because of presystemic conjugation and first-pass metabolism in the liver, the absolute bioavailability is only about 40%, showing a 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 estrogens, EE is biotransformed via (cytochrome P450-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 in the liver. In the urine mainly glucuronides, and in the bile and plasma, mainly sulphates are detected.

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

5.3 Preclinical safety data

The acute toxicity of estrogens is low. because of the pronounced differences between experimental animal species and humans, the results of animal studies with estrogens, can only be extrapolated to a limited extent to humans. Ethinylestradiol, a synthetic estrogen frequently used in hormonal 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 in rabbits at embryotoxic doses, and in mice even at the lowest dose tested (1 mg/kg/day). The significance of these findings regarding human use 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 SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate,
maize starch,
povidone K 30,
magnesium stearate.

Film-coating:
hypromellose
lactose monohydrate,
macrogol 6000,
propylene glycol,
talc,
titanium dioxide (E 171),
red iron oxide (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.

6.4 Nature and contents of container

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

6.5 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 45054, Jerusalem

9. MARKETING AUTHORISATION NUMBER(S)

127-34-30410-00

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