PACKAGE INSERT

1. BRAND OR PRODUCT NAME

Belara 0.03 mg/2 mg film-coated tablets

2. NAME AND STRENGTH OF ACTIVE SUBSTANCE

ethinylestradiol and chlormadinone acetate

3. PRODUCT DESCRIPTION

Round, pale pink, biconvex film-coated tablet.

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

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)

4. HARMACODYNAMICS/PHARMACOKINETICS

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations, ATC code: G03AA.

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 efficacy

In clinical studies in which the administration of Belara was tested for up to 2 years in 1655 women and more than 22 000 menstruation cycles, there were 12 pregnancies. In 7 women administration errors, concomitant diseases causing nausea or vomiting, or concomitant administration of medicines known to reduce the contraceptive effect of hormonal contraceptives were present in the period of conception.

Pearl index	**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]

4.2 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 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. On account of 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 estrogens, 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. In the urine mainly glucuronides, and in the bile and plasma mainly sulphates are found.

Elimination

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

4.3 Preclinical safety data

The acute toxicity of estrogens is low. On account of the pronounced differences between experimental animal species and in relation to humans, the results of animal studies with estrogens have only limited predictive value for humans. Ethinylestradiol, a synthetic estrogen 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.

5. INDICATION

Hormonal contraception.

6 RECOMMENDED DOSAGE

Dosage of the film-coated tablets

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 the 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.

7. MODE/ROUTE OF ADMINISTRATION

Starting the 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 day of the next menstruation. 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.

The first film-coated tablet can also be taken on the 2^{nd}-5^{th} day of menstruation, irrespective of whether bleeding has ceased or not. In this case additional mechanical contraceptive measures must be taken during the first seven days of administration.

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.

Switching from another hormonal contraceptive to Belara

Switching from another combined hormonal contraceptive
The woman should start taking Belara on the day following the usual tablet-free or placebo tablet interval of her previous combined hormonal contraceptive.

Switching from a progestogen-only pill ("POP")
The first Belara film-coated tablet should be taken on the day after stopping the progestogen-only preparation. During the first seven days additional mechanical contraceptive measures must be used.

Switching from a contraceptive hormone injection or implant
Administration of Belara can be started on the day of the removal of the implant or on the day of the originally planned injection. During the first seven days additional mechanical contraceptive measures must be used.

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 in the second trimester
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 the 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 11.)
Belara should not be taken by breast-feeding women.

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

Irregular tablet administration
If the user has forgotten to take a film-coated tablet, but takes it **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 management of missed tablets can be guided by the following two basic rules:
1. tablet-taking must never be discontinued for longer than 7 days
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

The last forgotten film-coated tablet should be taken immediately, even if this means taking two tablets at the same time. 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. If tablets were missed in week 1 of the cycle and intercourse took place in the seven days prior to the missing of tablets (including the tablet-free interval), the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

If the current pack contains less than seven tablets, the next pack of Belara must be started as soon as the current pack is finished, i.e. there should be no interval between the packs. 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.

Instructions in case 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 section "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).

8. CONTRAINDICATIONS

Combined oral contraceptives (COCs) must not be taken in the event of the diseases described below. Belara should be discontinued immediately if one of these conditions occurs during administration:
- previous or existing arterial or venous thrombosis (e.g. deep-vein thrombosis, pulmonary embolism, myocardial infarction, stroke);
- prodromal or first signs of thrombosis, thrombophlebitis or embolic symptoms (e.g. transient ischaemic attack, angina pectoris);
- scheduled surgery (at least four weeks in advance) and for the period of immobilisation, e.g. after accidents (e.g. plaster cast after accidents);
- diabetes mellitus with vascular changes;
- loss of control of diabetes mellitus;
- uncontrolled hypertension or a significant increase in blood pressure (values constantly above 140/90 mm Hg);
- hereditary or acquired predisposition for venous or arterial thrombosis, such as APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant);
- 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;
- a history of, or existing liver tumours;
- severe epigastric pain, enlargement of the liver, or symptoms of intra-abdominal haemorrhage (see section 12.);
- 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 hypertriglyceridemia;
- first-time symptoms of migrainous headache or more frequent occurrence of unusually severe headache;
- history of migraine with focal neurological symptoms ("migraine accompagnée");
- acute sensory disorders, e.g. visual or hearing disorders;
- motor disorders (particularly paresis);
- increase in epileptic seizures;
- severe depression;
- otosclerosis deteriorating during previous pregnancies;
- unexplained amenorrhoea;
- endometrial hyperplasia;

- unexplained genital bleeding;
- hypersensitivity to the active substances or to any of the excipients in section 3.

One severe risk factor or multiple risk factors for venous or arterial thrombosis may constitute a contraindication (see section 9.).

9. WARNINGS AND PRECAUTIONS

Warnings

Smoking increases the risk of severe cardiovascular side effects of the combined oral contraceptive (COC). 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.

COC administration is 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 morbidity and mortality risk.

In the presence of one of the following diseases/risk factors the advantage of Belara administration should be weighed up against the risks and these should be discussed with the woman before she starts taking the film-coated tablets. If these diseases or risk factors develop or deteriorate during administration, the user should consult her physician. The physician should then decide whether treatment is to be discontinued.

Thromboembolism and other vascular diseases
Results from epidemiological studies show that there is a connection between the administration of oral 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.

The use of combined oral contraceptives (COC) carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2%.

It is not known how Belara influences the risk of VTE compared with other combined oral contraceptives.

The risk of venous thromboembolism increases on the use of COCs with:
- increasing age;
- positive family history (venous thromboembolism in one of the siblings or parents at a relatively young age). If hereditary predisposition is suspected, it is advisable to refer the woman to a specialist before deciding on the use of a COC.
- long-term immobilisation (see section 8.);
- obesity (body mass index > 30 kg/m²).

The risk of arterial thromboembolism increases with:
- increasing age;
- smoking;
- dyslipoproteinaemia;
- obesity (body mass index > 30 kg/m²);
- hypertension;
- heart valve disease;
- atrial fibrillation;

- positive family history (arterial thromboembolism in one of the siblings or parents at a relatively young age) if hereditary predisposition is suspected, it is advisable to refer the woman to a specialist before deciding on the use of a COC.

Other diseases affecting blood circulation are diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and sickle-cell anaemia.

On consideration of the benefit/risk ratio it should be remembered that adequate treatment of the above diseases may reduce the risk of thrombosis.

The increased risk of thromboembolic events during puerperium should be taken into account.

There is no consensus on whether there is a connection between superficial thrombophlebitis and/or varicose veins and the aetiology of venous thromboembolism.

Possible symptoms of venous or arterial thrombosis are:
- pain and/or swelling in a leg;
- sudden severe chest pain, irrespective of whether it radiates to the left arm or not;
- sudden shortness of breath, sudden coughing of unknown cause;
- unexpectedly severe headache of long duration;
- partial or complete loss of vision, diplopia/speech disorders or aphasia;
- dizziness, collapse, in some cases including a focal epileptic seizure;
- sudden weakness or dysaesthesia on one side or one part of the body;
- motor disturbances;
- acute abdominal pain.

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

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Tumours
Some epidemiological studies indicate that the long-term use of oral 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 section "Medical examination").

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 COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC 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 COC users, the biological effects of COCs or a combination of both.

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 Diseases
Many women taking oral contraceptives had a slight increase in blood pressure; however, a clinically significant increase is rare. The connection between the administration of oral 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 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.

In women with a history of herpes gestationis there may be a recurrence during COC administration. In women with a history of hypertriglyceridaemia or a family history of such, the risk of pancreatitis is increased during COC administration. Acute or chronic disturbances of liver function may necessitate discontinuation of COC 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 COCs.

COCs 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 oral contraceptives.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions

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

- epilepsy;
- multiple sclerosis;
- tetany;
- migraine (see also section 8.);
- asthma;
- cardiac or renal insufficiency;
- Chorea minor;
- diabetes mellitus (see section 8.);
- liver diseases (see section 8.);
- dyslipoproteinaemia (see section 8.);
- auto-immune diseases (including systemic lupus erythematosus);
- obesity;
- hypertension (see section 8.);
- endometriosis;
- varicosis;
- phlebitis (see section 8.);
- blood coagulation disorders (see section 8.);
- mastopathy;
- uterine myoma;
- herpes gestationis;
- depression (see section 8.);
- chronic inflammatory bowel disease (Crohn´s disease, ulcerative colitis; see section 12.).

Medical examination

Before prescribing oral contraceptives a complete medical history of the woman and her family should be taken under consideration of the contraindications (see section 8.), risk factors (see section 9.) and a medical examination should be carried out. This should be repeated annually during Belara administration. A regular medical examination is also necessary because contraindications (e.g. transient ischaemic attacks) or risk factors (e.g. history of venous or arterial thrombosis in the family) may occur for the first time on administration of an oral contraceptive. The medical examination should include measurement of blood pressure, examination of the breasts, abdomen and internal and external genital organs and appropriate laboratory tests.

The woman should be informed that the administration of oral contraceptives, including Belara, does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

Impaired efficacy

Omission of 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 10.) 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 the 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 section "Irregular tablet administration", "Instructions in case of vomiting" and section 10.).

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 10.).

Effects on ability to drive and use machines
Combined oral contraceptives are not known to have negative effects on the ability to drive or to operate machines.

10. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Interactions of ethinylestradiol, the estrogen component of Belara, with other medicinal products may raise or reduce the serum concentration of ethinylestradiol. If long-term treatment with these active substances is necessary, non-hormonal contraceptive methods should be used. Reduced serum concentrations of ethinylestradiol may lead to increased frequencies of breakthrough bleeding and cycle disorders and impair the contraceptive efficacy of Belara; elevated serum levels of ethinylestradiol may lead to an increased frequency and severity of side effects.

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);
- active substances inducing microsomal enzymes in the liver, such as rifampicin, rifabutin, barbiturates, antiepileptics (such as carbamazepine, phenytoin and topiramate), griseofulvin,

barbexaclone, primidone, modafinil, some protease inhibitors (e.g. ritonavir) and St. John's wort (see section 9.);
- certain antibiotics (e.g. ampicillin, tetracycline) in some women, possibly due to the reduction of enterohepatic circulation by estrogens.

On concomitant short-term treatment with these medicinal products/active substances and Belara additional mechanical contraceptive methods should be used during treatment and the first seven days afterwards. With active substances that reduce the ethinylestradiol serum concentration by inducing hepatic microsomal enzymes, additional mechanical contraceptive methods are to be used up to 28 days after termination of treatment.

If concomitant medicinal product administration runs beyond the end of the tablets in the COC blister pack, the next COC pack should be started without the usual tablet-free interval.

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

Ethinylestradiol may affect the metabolism of other substances
- by inhibiting hepatic microsomal enzymes and consequently raising the serum concentration of active substances such as diazepam (and other benzodiazepines metabolised by hydroxylation), ciclosporin, theophylline and prednisolone;
- by inducing hepatic glucuronidation and consequently reducing serum concentrations of e.g. clofibrate, paracetamol, morphine and lorazepam.

Insulin or oral antidiabetic requirements may be altered due to effects on glucose tolerance (see section 9.).

This may also apply to medicines taken recently.

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

Laboratory tests
During administration of COCs the results of certain laboratory tests may be affected, including hepatic, adrenal and thyroid function tests, plasma levels of carrier proteins (e.g. SHBG, lipoproteins), parameters of carbohydrate metabolism, coagulation and fibrinolysis. The nature and extent are partially dependent on the nature and dose of the hormones used.

11. USE DURING PREGNANCY/LACTATION

Belara is not recommended 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 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 reproduction toxicity (see section 8.), clinical data of more than 330 exposed human pregnancies did not show any embryotoxic effects of chlormadinone acetate.

Lactation may be affected by estrogens 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 child. Therefore Belara should not be used during lactation.

12. ADVERSE EFFECTS/UNDESIRABLE EFFECTS

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

b) The following side effects have been reported after administration of Belara in a clinical study with 1629 women.

Frequency of ADRs / *System Organ Class*	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1/1000)**	**Very rare (< 1/10 000)**
Immune system disorders			drug hypersensitivity including allergic skin reactions		
Psychiatric disorders		depressed mood, nervousness			
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	
Vascular disorders				hypertension, hypotension, circulatory collapse, varicose vein, venous thrombosis*	
Gastrointestinal disorders	nausea	vomiting	abdominal pain, abdominal distension, diarrhoea		
Skin and subcutaneous tissue disorders		acne	pigmentation disorder, chloasma, alopecia, dry skin	urticaria, eczema, erythema, pruritus, aggravated psoriasis, hypertrichosis	erythema nodosum
Musculoskeletal and connective tissue		sensation of heaviness	back pain, muscle disorders		

* see section c)

disorders					
Reproductive system and breast disorders	vaginal discharge, dysmenorrhoea, amenorrhoea	lower abdominal pain	galactorrhoea, fibroadenoma of breast, vaginal candidiasis	breast enlargement, vulvovaginitis, menorrhagia, premenstrual syndrome	
General disorders and administration site conditions		irritability, fatigue, oedema, increased weight	decreased libido, hyperhidrosis	increased appetite	
Investigations		increase in blood pressure	changes in blood lipids including hyper-triglyceridaemia		

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

- The administration of combined oral contraceptives is known to be associated with an increased risk of venous and arterial thromboembolism (e.g. venous thrombosis, pulmonary embolism, stroke, myocardial infarction). This risk may also be increased by additional factors (see section 9.).
- An increased risk of biliary tract diseases has been reported in some studies on the long-term administration of COCs.
- 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 9.).
- Aggravation of chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis; see section 9.)
- Ovarian cyst, vaginal dryness, myelitis, influenza-like symptoms.

For other serious side effects such as cancer of the cervix or breast see section 9.

13. OVERDOSE AND TREATMENT

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.

14. INCOMPATIBILITIES

Not applicable.

15. STORAGE CONDITION

Shelf life: 2 years.

Special precautions for storage: Do not store above 30°C.

Special precautions for disposal and other handling: No special requirements.

16. DOSAGE FORMS OR PRESENTATION

1x21 or 3x21 film-coated tablets are packed into PVC/PVDC//Al or PP//Al or PP//PP blister pack and cardboard box.
Not all presentations may be available locally.

17. NAME AND ADDRESS OF MANUFACTURER OR PRODUCT OWNER OR PRODUCT LICENCE HOLDER

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

18. DATE OF REVISION OF PACKAGE INSERT

11.09.2015