פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

Belara

1. Name of the Medicinal Product

BELARA®

2. Prescription Status/Pharmacy Only

Prescription-only

3. Composition of the Medicinal Product

3.1 Substance or Indication Group

Sex hormones

3.2 Qualitative and Quantitative Composition

- Active ingredients

One pack of BELARA contains 21 film-coated tablets each of 0.03 mg ethinyl oestradiol and 2 mg chlormadinone acetate

- Other ingredients

Lactose monohydrate, maize starch, povidone K 30, magnesium stearate, hypromellose, macrogol 6000, propylene glycol, talc, titanium dioxide (E 171), red iron oxide (E 172).

Belara contains 69.545mg lactose monohydrate per tablet.

4. Indications

BELARA is a hormonal contraceptive to be taken by mouth. If such oral contraceptives contain two hormones like Belara, they are also called “combined oral contraceptives” (COC). The 21 tablets of a cycle pack contain the same amounts of both hormones, and therefore Belara is also called a “monophasic preparation”.

Oral contraceptives like Belara will not protect you against AIDS (HIV infection) or other sexually transmitted diseases. Only condoms can help to do this.

5. Contraindications

Pregnancy

Pregnancy should be excluded before starting treatment with BELARA. If pregnancy occurs during the use of BELARA, treatment should be discontinued immediately. Previous use of BELARA, however, does not justify termination of pregnancy.

Use during lactation

If BELARA is taken during lactation it should be remembered that milk production may be reduced. Very small amounts of the active ingredients are excreted in breast milk.
Generally, however, contraception is only indicated during prolonged lactation periods since a cycle does not usually occur during short lactation periods.
If possible, non-hormonal methods of contraception should be used until the infant has been completely weaned.

Liver diseases

- Acute and chronic progressive liver diseases, disorders of biliary bilirubin secretion (Dubin-Johnson and Rotor’s syndrome), biliary secretion disorders, bile flow disorders (cholestasis, including in the past, if associated with a pregnancy or the use of sex steroids (sex hormones); this includes idiopathic jaundice or pruritus during a previous pregnancy or oestrogen-progestogen treatment).
- After resolution of viral hepatitis (liver tests normal), a period of about six months should be allowed to elapse before initiating treatment.
- Past or existing liver neoplasms.

Vascular and metabolic diseases

- Smokers (see "Warnings“)
- Previous or existing thrombo-embolic disorders (especially stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism) as well as states that increase susceptibility to these conditions (e.g. disorders of the coagulation system with a tendency to thrombus formation, congenital AT III, protein C and protein S deficiency, certain cardiac diseases)
- Arterial hypertension requiring treatment
- Severe diabetes (mellitus) with associated vascular changes (micro-angiopathy)
- Sickle-cell anaemia
- Severe disorders of lipid metabolism, especially when accompanied by other risk factors for cardiovascular disorders

Malignancy

- Certain malignant tumours (e.g. of the breast, uterine cervix or uterine mucosa), also after their treatment or suspected cases

Endometrial hyperplasia

Other diseases

- History of gestational herpes
- Otosclerosis with deterioration during previous pregnancies
- Severe obesity
- Migraine associated with sensory, perceptual and/or motorial disorders (migraine accompagnée)
- Undiagnosed abnormal genital bleeding
- Hypersensitivity to one of the ingredients of BELARA
- Itching all over the body or bile flow disorder, particularly if this occurred in connection with a previous pregnancy or oestrogen treatment
- Previous or existing inflammation of the pancreas and this is associated with severe increase in blood fats (triglycerides)
- Severe depression
- No period from unknown reasons

Reasons for immediate discontinuation

- Onset of pregnancy
- Initial signs of thrombophlebitis or thromboembolic manifestations
- Planned surgery (6 weeks beforehand) and for the duration of immobilisation, for example after accidents (e.g. plaster casts)
- First occurrence of migraine-like or increased frequency of unusually severe headache
- Acute sensory deficits (visual, auditory disorders etc.)
- Motorial disorders (especially paralysis)
- Severe upper abdominal complaints, hepatomegaly or signs of intra-abdominal bleeding (see also "Side-effects/upper abdominal complaints“)

- Rise in blood pressure to levels constantly above 140/90 mmHg
- Jaundice, hepatitis, generalised pruritus, cholestasis and abnormal liver function tests
- Increase in epileptic seizures
- First onset or recurrence of porphyria (all three forms, especially acquired porphyria)
- Acute decompensation of diabetes mellitus

States requiring special monitoring

- Cardiac and renal diseases, migraine, epilepsy, asthma (also in the past), since these conditions may be affected by possible accumulation of fluid
- History of phlebitis
- Marked tendency to varicosity
- Multiple sclerosis
- Sydenham's chorea
- Tetany
- Diabetes mellitus and tendency to this disorder
- Past history of liver diseases
- Lipid metabolism disorders
- Considerable overweight
- Blood pressure elevation
- Endometriosis
- Mastopathy
- Otosclerosis
- Uterus myomatosus

- Diseases of the immune system (including systemic lupus erythematosus)

- Chronic inflammation of the bowels (Crohn's disease, ulcerative colitis)

6. Side-effects

General side-effects

- Feeling of breast tension
- Changes in weight
- Depression
- Changes in libido
- Gastric complaints
- Nausea, emesis
- Headache, also migraine-like
- Reduced tolerance to contact lenses
- After long-term use, particularly susceptible women may occasionally develop patchy facial skin discoloration (chloasma) which is exacerbated by prolonged sun bathing. Women with a tendency to such changes should avoid excessive exposure to sunlight.
- Certain vaginal infections such as candidiasis occasionally occur.
- Vaginal discharge
- Pain during menstruation
- Irritability
- Nervousness
- Dizziness
- Visual disorders
- Acne
- Pain in the belly
- Tiredness
- Feeling of heaviness in the legs
- Diarrhoea
- Hair loss
- Dry skin
- Back pain
- Muscle problems
- Tendency to sweat
- Changes in blood fats including increased triglycerides

Rare:

- Conjunctivitis
- Deafness
- Tinnitus
- High blood pressure
- Low blood pressure
- Blood circulation collapse
- Hives
- Eczema
- Itching
- Worsening of psoriasis
- Excessive hair on the body or in the face
- Increased appetite
- Skin rash and erythema nodosum have been observed (very rare).

Cycle-specific side-effects

- Intracyclic menstrual bleeding:
  Spotting and breakthrough bleeding (of menstrual intensity) may occur during the use of BELARA. Intracyclic bleeding of this kind is observed rarely and almost only during the first few medication cycles. In these cases patients should continue taking BELARA. If the bleeding does not cease spontaneously within a few days, it can usually be stopped by additionally administering 20-40 µg ethinyl oestradiol for 4-5 days (but not beyond the last tablet of a pack). If bleeding still persists or is repeated during several cycles, a thorough examination is recommended to exclude organic pathology.

- Absence of withdrawal bleeding:
  If in very rare cases withdrawal bleeding does not occur during the medication-free days, patients can continue taking BELARA if pregnancy is ruled out within the first 10 days of the new medication cycle.

  Note:
  After discontinuation of BELARA in most cases the reproductive glands rapidly resume their full function and the ability to conceive is restored. The first cycle is usually prolonged by about 1 week.

Upper abdominal complaints, liver and gallbladder

There is a slightly increased incidence of biliary tract diseases during the long-term use of hormonal contraceptives. Opinion is divided regarding the possibility of gallstone formation during the use of oestrogen-containing contraceptives.

In rare cases benign, and even more rarely malignant liver tumours have been observed after the use of hormonal agents of the kind contained in this product, and in some cases have resulted in potentially fatal intra-abdominal bleeding.

If unusual upper abdominal complaints develop that do not rapidly resolve spontaneously, it may be necessary to discontinue treatment.

In very rare case the symptoms described may also occur in association with hepatic vein or mesenteric vein thrombosis.

Interactions with laboratory tests

Some laboratory tests on liver, adrenal and thyroid functions, certain blood proteins, carbohydrate metabolism and blood clotting may be affected by the administration of Belara.

Effect on mammary tissue

Breast cancer is one of the hormone-dependent malignancies. Risk factors for breast cancer such as early menarche, late menopause (after the 52nd year), nulliparity, anovulatory cycles etc. are well known and suggest the possibility of hormonal involvement in the development

of breast cancer. Hormone receptors are of central importance in the tumour biology of breast cancer. Especially oestrogens induce a multiplicity of growth factors such as transforming growth factor alpha (TGF-alpha). Oestrogens and progestogens influence the growth of breast cancer cells. These tumour-biological relationships, among others, form the theoretical basis for the pharmacological treatment of postmenopausal receptor positive breast cancer. Analysis of epidemiological studies that indicate a possible relationship between the use of oral contraceptives and breast cancer also suggest that the occurrence of breast cancer in women up to middle age is relatively frequently associated with early initiated, long-term use of oral contraceptives. On the other hand, this is only one of several possible risk factors.

During the course of 10 years after cessation of COC use the increased risk of breast cancer gradually returns to the age-related background risk. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer.

Breast secretion and enlargement has been observed in individual cases.

Effect on the neck of the womb

Some studies show that there is a risk factor for cancer of the neck of the womb, if women whose neck of the womb is infected by a certain sexually transmitted virus (human papilloma virus) take the pill for a long time. However, it is unclear to what extent these results are affected by other factors (e.g. different in the number of sexual partners or in the use of mechanical contraceptive methods).

Ovarian cysts

Functional ovarian cysts have been found in women taking oral contraceptives.

Thrombo-embolic risk

The use of hormonal contraceptives is associated with an increased risk of venous and arterial thrombo-embolic diseases (e.g. venous thrombosis, pulmonary embolism, stroke, myocardial infarction). This risk can be further increased by additional factors (smoking, hypertension, disorders of blood coagulation or lipid metabolism, considerable overweight, varicose veins, history of phlebitis and thrombosis) (see "Warnings“).

Other diseases

Many women have a slight increase in blood pressure while taking oral contraceptives. If the blood pressure rises considerably while taking Belara, a discontinuation of taking Belara and a medicine to lower the blood pressure are required. As soon as the blood pressure has returned to normal, it is possible to take Belara again.

Women that have suffered from herpes during a previous pregnancy, this may recur during the use of an oral contraceptive.

7. Interactions with Other Drugs

The contraceptive effectiveness of this product may be impaired by the concomitant administration of drugs that increase the biodegradation of steroid hormones, e.g. barbiturates, rifampicin, rifabutine, griseofulvin, modafinil, phenylbutazone, certain medicines for treatment of HIV infection (e.g. ritonavir) and anti-epileptic agents (such as barbexaclone, carbamazepine, phenytoin, primidone, topiramate) and preparations containing St-John's-Wort. Spotting has been reported in women taking preparations containing St-John's-Wort and oral contraceptives at the same time. Reduced drug levels have also been measured due to changes in intestinal flora associated with the concomitant use of antibiotics such as ampicillin or tetracyclines, medicines that stimulate bowel movement (e.g. metoclopramide) and also after the ingestion of activated charcoal. Both increased rates of intermenstrual bleeding and, in isolated cases, pregnancies have been recorded.

Insulin or oral antidiabetic requirements may be altered due to an influence on glucose tolerance.

The excretion of diazepam, ciclosporin, prednisolone and theophylline or caffeine is reduced during the use of oral contraceptives, with the result that the effect of these active substances may be increased and prolonged.

The effect of preparations containing clofibrate, paracetamol, morphine or lorazepam may be reduced if taken during the use of oral contraceptives.

8. Warnings

Because of the possibility of severe health impairment due to thrombo-embolic events (see "Side-effects“), users should be carefully screened for the presence of predisposing factors (e.g. varicose veins, history of phlebitis and thrombosis as well as heart diseases, considerable overweight, disorders of blood coagulation) and for the occurrence of venous thrombo-embolic events among close relatives at an early age and any such factors should be taken into account when deciding whether to prescribe this medication.

Smokers taking hormone-containing preparations for contraceptive purposes have an additionally increased risk of developing sometimes serious sequelae of vascular changes (e.g. myocardial infarction, stroke). The risk increases with age and rising cigarette consumption.

Especially women over the age of 30 years should therefore refrain from smoking if they intend to take hormone-containing medications for the prevention of pregnancy. If they are unable to stop smoking, other forms of contraception should be used.

Postmarketing surveillance studies have shown that the incidence of thrombo-embolic diseases may possibly decrease during the use of preparations with a low-dose oestrogen component (0.05 mg or less), which led to the development of low-dose hormonal contraceptive preparations. Whether the expectation that women taking such low-dose preparations do in fact have a lower incidence of thrombotic or thrombo-embolic vascular occlusions is justified has not yet been conclusively established.

Therefore, even when taking low-dose hormonal contraceptives, patients should be carefully screened for the presence of factors promoting thrombo-embolic processes (see above) and the risk should be weighed against the potential benefits of this method of contraception.

The occurrence of thrombo-embolic diseases in relatives at an early age may indicate the presence of disorders of the coagulation system. Diseases of this kind include deep vein thrombosis, pulmonary embolism, stroke, sudden disorders of sensation and perception (visual, auditory disorders), speech disorders and disorders of movement, especially paralysis, myocardial infarction and angina pectoris. If there is a family history of such illnesses, the patient's coagulation status should be carefully ascertained before prescribing BELARA (this includes, for example, determinations of AT III, protein C and protein S).

Women over 40 years of age require special monitoring since the tendency to thrombosis increases with age.

The use of any combined oral contraceptive carries an increased risk of venous thrombo-embolism (VTE) compared with not taking a combined oral contraceptive. 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% of cases.
It is not known how BELARA influences the risk of VTE compared with other combined oral contraceptives.

Pathological conditions that may deteriorate during treatment with BELARA:

Certain illnesses may be adversely affected both by pregnancy and by the use of oestrogens or oestrogen-progestogen combinations. These conditions include epilepsy, multiple sclerosis, otosclerosis, gestational herpes, porphyria, tetanus, candidiasis and trichomonal infections.

Patients with asthma, migraine and severe cardiac or renal dysfunction require particularly close medical monitoring due to the possibility of fluid retention when taking oestrogen-progestogen combinations (see also "States requiring special monitoring" in "5. Contraindications").

9. Principal Incompatibilities

No incompatibilities are known.

10. Single and Daily Dosage

One tablet should be taken every day at the same time, preferably before bedtime. The tablets are to be swallowed whole.

11. Mode and Duration of Administration

Before initiating treatment with hormonal contraceptives, a thorough general and gynaecological examination should be carried out, in which special emphasis should be placed on excluding pregnancy. If pregnancy occurs during the use of BELARA, the medication is to be discontinued. Previous intake of BELARA, however, does not justify termination of pregnancy.

Check-ups should be performed at intervals of about six months during the use of BELARA.

For users starting on or changing to BELARA, regular intake begins with the first tablet on the first day of the cycle, which corresponds to the first day of menstrual bleeding.

If BELARA is taken at the first onset of bleeding after childbirth, there may be no reliable contraceptive protection during the first two weeks since it may no longer be possible to suppress this ovulation.

If Belara is taken immediately after a miscarriage or abortion in the first three months of pregnancy, there is no need to use any additional contraceptive methods.

If childbirth or miscarriage occurs in the second three months of pregnancy (without breast-feeding) it is possible to take Belara 21-28 days after birth and there is no need to use any additional mechanical contraceptive methods. If, however, more than 28 days have passed since birth, the women must use additional mechanical contraceptive methods for the first seven days.

The first pill should be pressed out at the position in the pack which is marked with the corresponding weekday (e.g. "Sun" for Sunday) and swallowed whole. Then one further pill should be taken daily following the direction of the arrows, if possible at the same time of day – preferably in the evening – since regularity of intake is essential to ensure the contraceptive reliability of BELARA. The interval between taking two tablets should regularly be 24 hours as far as possible. The weekdays printed on the pack allow the user to check every day whether the pill for the day in question has already been taken.

Intake of the last pill is followed by a seven-day medication-free interval during which bleeding occurs within 2-4 days after the last pill.

After the seven-day medication-free interval, medication should be continued with the next BELARA pack, regardless of whether the bleeding has already ceased or is still persisting.

Important (contraceptive reliability)

Contraceptive protection commences with the first day of intake and continues during the seven-day medication-free periods (exceptions: after childbirth, miscarriage - see above).

Intake errors, vomiting or intestinal diseases associated with diarrhoea, prolonged concomitant administration of certain drugs (see "Interactions with Other Drugs") and very rare individual metabolic disorders may impair contraceptive effectiveness. Mild laxatives do not affect contraceptive reliability.

If a user has ***forgotten*** to take a pill at the usual time, it must be taken within the following 12 hours at the latest. If the usual intake interval is exceeded by more than 12 hours, effective contraception is no longer guaranteed during this cycle. In such cases users should continue taking pills from the current calendar pack as

scheduled, but leaving out the pill that has been forgotten in order to prevent premature bleeding. Mechanical protective measures should also be taken.

In the event of *vomiting* or *intestinal upsets* medication intake should not be interrupted. Additional mechanical protective measures should be taken during the cycle concerned.

12. Emergency Measures, Symptoms and Antidotes

Symptoms of intoxication

Acute intoxication resulting from the simultaneous intake of a large number of tablets is only to be expected in extreme cases and does not result in life-threatening conditions, but mainly in gastrointestinal complaints, impairment of hepatic function, water balance and electrolyte metabolism, as well as withdrawal bleeding in women. Prepubertal girls may experience slight vaginal bleeding.

Treatment of intoxication

Preventive monitoring of the electrolyte metabolism, water balance and hepatic function as well as symptomatic measures are only necessary in rare cases.

13. Pharmacological and Toxicological Characteristics, Pharmacokinetics and Bioavailability Data Relevant for Therapeutic Use

13.1 Pharmacological Characteristics

Contraception

The continuous intake of BELARA over 21 days results in inhibition of pituitary FSH and LH secretion with associated suppression of ovulation. The consistency of cervical mucus is changed. This reduces sperm migration to the cervical canal and alters sperm motility.

Dermatology

The known effect of chlormadinone acetate on androgenic skin changes such as acne and seborrhoea has been observed during tolerability and efficacy studies.

13.2 Toxicological Characteristics

Because of the pronounced differences between experimental animal species and between these species and humans, the results of laboratory animal studies with progestogens have only limited predictive value for humans.

Acute and chronic toxicity

The acute toxicity of ethinyl oestradiol and chlormadinone acetate after oral intake is low; more than 1 g/kg of either drug is tolerated without serious symptoms. Toxicity studies with repeated administration of ethinyl oestradiol and other oestrogens produced various findings – including increased mortality, haematological disorders, reduced gonad weight, pituitary tumours – which on the basis of existing experience are not predictive for clinical therapy.

Administration of high-dose chlormadinone acetate alone or in combination with ethinyl oestradiol resulted in a number of findings (reduced weight of female gonads, adrenals and pituitaries, increase in liver weight etc.) that could be interpreted as evidence of increased pharmacodynamic effects.

Reproductive toxicity

Oestrogens have embryotoxic and embryolethal effects in laboratory animals and cause an increased rate of abortions. The embryolethal effect of ethinyl oestradiol is dose-dependent. Ethinyl oestradiol crosses the placenta and enters the foetus. Newborn male mice exposed to ethinyl oestradiol during gestation had focal Leydig cell hyperplasia in the gonads. Ethinyl oestradiol impaired migration of ovum in Rhesus monkeys. Experience with the use of ethinyl oestradiol in humans during pregnancy has not so far yielded any evidence of congenital deformities or other impairments. High doses of ethinyl oestradiol may result in the loss of embryos that have not yet become implanted in the first week after conception.

High doses of chlormadinone acetate have reportedly been associated with embryolethal effects and cleft palate in mice and rabbits. In low doses (up to 3 mg/kg) chlormadinone acetate did not have any specific teratogenic effects.

Virilising effects occasionally observed in association with progestogen administration during pregnancy are unlikely with chlormadinone acetate. Possible antiandrogenic (feminising) effects are slight compared to those of other anti-androgens.

Mutagenic and tumorigenic potential

Evaluation of ethinyl oestradiol and chlormadinone acetate in a recognised standard test battery yielded no evidence of relevant mutagenic properties. In other studies, however, chlormadinone acetate caused DNA adduct formation and an increase in DNA repair synthesis in cultured human liver cells; similar studies in rat liver cells revealed only very minor effects. Administration of chlormadinone acetate to rats in vivo caused only very slight DNA adduct formation and no increase in DNA repair synthesis was observed.

The clinical relevance of these findings is questionable. Existing clinical experience has not shown an increased incidence of liver tumours in man. Long-term studies in rats and mice have not yielded any evidence that chlormadinone acetate is potentially tumorigenic.

Ethinyl oestradiol may increase the incidence of benign pituitary tumours, malignant mammary, uterine and cervical tumours in mice and the incidence of liver tumours in rats. Ethinyl oestradiol also increased the rate of malignant mammary tumours in female rats. The incidence of renal tumours in hamsters with ethinyl oestradiol is lower than with other natural or synthetic oestrogens.

In humans, oestrogen-progestogen combinations for hormonal contraception appear to have a generally variable impact on tumour development. While existing findings suggest that the incidence of ovarian cancer, endometrial cancer and benign mammary tumours is decreasing in contraceptive users, there is an increased risk for the development of generally rare benign and malignant liver tumours and a possibly increased risk of cervical carcinoma and dysplasia. The results of epidemiological studies also show that women have a slightly increased risk of developing breast cancer during the use of oral contraceptives and for up to 10 years thereafter, although it is still not clear whether the elevated risk is

attributable to earlier diagnosis of breast cancer or is the result of biological effects of contraceptive hormones.

13.3 Pharmacokinetics

Chlormadinone acetate and ethinyl oestradiol are absorbed rapidly and almost completely after ingestion of BELARA tablets. The systemic availability of chlormadinone acetate is high compared to that of ethinyl oestradiol, since it is not subject to first-pass metabolism. Peak plasma concentrations are reached 1-2 hours after oral administration. In the plasma the active substances are mainly protein-bound proteins. Both agents are rapidly distributed to tissues. Chlormadinone acetate is stored primarily in fatty tissue, from which it is steadily released back into the circulation. Steady state is reached after 3-4 days for ethinyl oestradiol and after 8 days for CMA. The mean elimination half-life of CMA is 34 hours, and that of ethinyl oestradiol 13-27 hours. Most of the chlormadinone acetate is excreted in the form of highly polar metabolites and conjugates in the urine and faeces in the ratio 40 : 60. Ethinyl oestradiol is also eliminated renally and faecally (40 : 60) with a mean renal half-life of 25 hours. Biodegradation products in the urine are predominantly glucuronide sulphates, while about 20% of the parent compound is recovered in the faeces.

14. Other Points

Check-ups

Before starting treatment, patients should be given a thorough general medical (including measurement of blood pressure, body weight, test for urinary glucose and, if necessary, specific liver diagnostic tests) and gynaecological examination (including the breasts and a cytological smear) in order to detect diseases requiring treatment and risk states, and above all to rule out pregnancy. These check-ups should be carried out about every six months during treatment.

Patients with clinically overt diabetes or a predisposition to this disorder should be monitored for possible changes in carbohydrate metabolism before and during treatment.

The influence of hormone therapy on the monitored parameters should always be taken into account when interpreting the results of liver function tests and endocrine assays. Unbiased results are generally not obtained until 2-4 months after the end of treatment.

Contraceptive reliability

As with all ovulation inhibitors, intake and method errors may occur and therefore 100% efficacy cannot be expected.

15. Shelf-life

BELARA has a shelf-life of 36 months and should not be used after the expiry date printed on the pack.

16. Special Storage Instructions

Do not store above 30˚C.

17. Formulations and Presentations

Pack with 1 x 21 tablets
Pack with 3 x 21 tablets

18. Date of Issue

November 2008

19. Manufacturer

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

Importer: TEC-O-PHARM-LIBRA LTD.

P.O.Box 45054 Jerusalem 91450, Israel.

BEL-LFP-0909-02