REGISTERED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

MINERVA-35

Tablets

COMPOSITION

The 28-day pack (Every-Day pack) contains 21 hormonal tablets, each with cyproterone acetate (6-chloro-17-hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione-acetate) 2 mg and ethinylestradiol (17α-ethinyl-estra-1,3,5(10)-triene-3,17β-diol) 0,035 mg, plus 7 non-hormonal tablets.

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.2 Progesterones with estrogens.

PHARMACOLOGICAL ACTION

The substance cyproterone acetate contained in Minerva-35 blocks the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. The stimulating effect of male sex hormones on androgen-dependent structures and functions is weakened or abolished by cyproterone acetate.

Excessive sebaceous gland function is decreased.

Apart from the described anti-androgen effect, cyproterone acetate also has a progestational action. The ethinylestradiol in the combination inhibits ovulation and changes the cervical mucus and the endometrium rendering them unfavourable for sperm penetration and nidation of a fertilised ovum, respectively.

INDICATIONS

Androgen-dependent acne, especially those forms which are accompanied by seborrhoea or by inflammation or formation of nodes (acne papulopustulosa, acne nodulocystica), androgen-dependent alopecia and mild forms of hirsutism.

Oral contraception in women requiring anti-androgen therapy.

CONTRA-INDICATIONS

Pregnancy; lactation; severe disturbances of liver function; recurrent cholestatic jaundice; jaundice or persistent itching during a previous pregnancy; Dubin-Johnson syndrome; Rotor syndrome; previous or existing liver tumours; existing or previous thromboembolic processes in arteries or veins and states which predispose to such diseases (eg disturbances of the clotting system with a tendency towards thrombosis, certain heart diseases); severe migraine or cerebrovascular insufficiency; sickle-cell

anaemia; existing or treated cancer of the breast or the endometrium; undiagnosed vaginal bleeding; severe diabetes with vascular changes; disturbances of lipometabolism; a history of herpes of pregnancy; otosclerosis with deterioration in previous pregnancies.

Strict medical supervision is required in patients with diabetes or a tendency to diabetes, high blood pressure, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, epilepsy, porphyria, tetany, chorea minor, asthma, depression, or states in which fluid retention occurs.

Reasons for immediate discontinuation of Minerva-35

Occurrence for the first time of migrainous headaches or more frequent occurrence of unusually severe headaches, sudden perceptual disorders (eg disturbances of vision or hearing), first signs of thrombophlebitis or thromboembolic symptoms (for example, unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason), a feeling of pain and tightness in the chest, pending operations (six weeks beforehand), immobilisation (for instance following accidents). In all these cases there may be an increased risk of thrombosis. Further reasons for discontinuation are: onset of jaundice, onset of hepatitis, itching of the whole body, significant rise in blood pressure, pregnancy.

WARNING

Minerva-35 is not for use in men and should not be used in children.

DOSAGE AND DIRECTIONS FOR USE

Before starting Minerva-35, a thorough gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (eg deep vein thrombosis, stroke, myocardial infarction) already at a young age. Pregnancy must be excluded. If the hirsutism has only recently appeared or has lately intensified to a considerable extent, an androgen-producing tumour or an adrenal enzyme defect must be excluded in the differential diagnosis.

Initial course

The first course of Minerva-35 is started on the first day of the cycle (the first day of the menstrual bleeding is counted as day 1 of the cycle). The first tablet should be taken from the starter section of the calendar pack by selecting the appropriate tablet for that day of the week (eg "Mon" for Monday). The tablet is swallowed whole with a little liquid. It does not matter at what time of the day the tablet is taken, but once the patient has selected a particular time, the tablet should be taken as near as possible at the same time each day. A tablet is then taken every day in the direction shown by the arrows until the pack is empty.

If the patient is using hormonal contraceptives, the doctor should decide when she should start treatment. The same applies to patients who have just had a delivery or an abortion.

The first cycle may be somewhat shorter than usual, whereas all following cycles will last four weeks.

An additional, non-hormonal method of contraception (with the exception of the rhythm and temperature methods) should be employed during the first 14 days of the first treated cycle.

Subsequent courses

After the last tablet has been taken from the first pack, tablet-taking is continued from a new pack on the very next day. The first tablet must again be taken from the starter section of the calendar pack marked with the appropriate day of the week.

Length of use

The length of use depends on the severity of the clinical picture. In general, treatment should be carried out over several months. It is recommended that Minerva-35 be taken for at least another 3 to 4 cycles after the signs have subsided. Should there be a recurrence weeks or months after discontinuation of tablet-taking, treatment with Minerva-35 may be resumed.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (after approximately day 45 of gravidity) could lead to signs of feminisation in male foetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminisation. However, pregnancy is a contra-indication for the use of Minerva-35.

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, there is some evidence of genotoxicity as further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. This DNA adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. One in vivo consequence of cyproterone acetate treatment was the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats.

The clinical relevance of these findings and how these findings relate to the risk of developing benign and malignant liver tumours in humans is presently unknown. Clinical experience to date would not support an increased incidence of hepatic tumours in man. Nor did investigations into the tumorigenicity of cyproterone acetate in rodents reveal any indication of a specific tumorigenic potential. However, it must be borne in mind that sexual steroids such as the substances contained in Minerva-35 can promote the growth of certain hormone-dependent tissues and tumours.

The incidence of diseases of the circulatory system in women using combined oral contraceptives is significantly greater than those of controls, and the mortality is slightly increased. Coronary thrombosis, cerebrovascular accidents and venous thrombosis are more likely to occur in women aged 35 years or over, particularly if they have used the contraceptive for longer than 5 years, if they smoke, if they are obese or if they are hypertensive. Additional risk factors are diabetes, hypercholesterolaemia and familial hyperlipoproteinaemia. However, the risk of mortality due to oral contraceptives in women under 35 who are in the high-risk group is in general far less than the risk of mortality due to pregnancy.

Hypertension may occur in association with the use of oral contraceptives. Regular blood-pressure checks, including a pretreatment level, are advisable.

Prolonged amenorrhoea following the use of oral contraceptives may occur. Caution is advised where oligomenorrhoea or amenorrhoea have occurred in the past.

Side-effects such as nausea, vomiting, headaches, mood changes, changes in libido, weight gain, skin pigmentation, poor tolerance of contact lenses, vaginal candidiasis, gall-bladder disease, gastro-intestinal irritation, fluid retention, tightness and tenderness of the breasts may occur.

In rare cases benign, and in even rarer cases malignant, liver tumours leading in isolated cases to life-threatening intraabdominal haemorrhage, have been observed after the use of hormonal substances such as those contained in Minerva-35. If severe upper abdominal complaints, liver enlargement or signs of intraabdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

Surgery is more likely to be associated with an increased incidence of thrombotic side-effects. Adequate precaution should be taken. Under no circumstances should the oral contraceptive tablet be stopped without having adopted a satisfactory alternative method of contraception.

If the patient forgets to take her tablet at the usual time, she must take it within the next 12 hours at the latest. If more than 12 hours elapse from the time that she normally takes her tablet, and also in the case of vomiting or diarrhoea, she must continue to take the other tablets in the pack at the usual time in order to avoid a premature withdrawal bleeding during this cycle. At the same time, however, an additional, non-hormonal method of contraception (with the exception of the rhythm and temperature methods) must be employed in order to prevent a pregnancy which would be a compelling reason for the discontinuation of Minerva-35 treatment.

Control examinations are recommended at about 6-monthly intervals during the use of Minerva-35.

If an intermenstrual bleeding occurs during the 3 weeks in which the beige tablets are being taken, their use should not be interrupted. A slight bleeding (spotting) will usually stop spontaneously. However, if the bleeding is heavy, similar to a menstrual bleeding, then a thorough examination is indicated to exclude organic factors.

If bleeding fails to occur while the tablets from the starter section are being taken, tablet-taking must provisionally be stopped and the doctor must be consulted.

Interaction with other medicines and efficacy

The efficacy of the contraceptive pill may be decreased in the case of irregular tablet-taking or when it is administered concomitantly with other medicines such as the anti-epileptic agents, antibiotics, barbiturates and rifampicin, and in patients with very rare individual metabolic disturbances (possible first symptom: intermenstrual bleeding). Mild laxatives do not impair the action of the tablets.

Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception should be recommended for the duration of antibiotic therapy and for seven days afterwards. Those on long-term antibiotic therapy need only take extra precautions for the first two weeks of antibiotic therapy.

Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.

With vomiting or diarrhoea, the absorption of oral contraceptives may be diminished and women should be advised to use additional methods of contraception at the time of such disorders in order to prevent a possible pregnancy, which would be a compelling reason for the discontinuation of Minerva-35 treatment.

Insulin and other hypoglycaemic requirements may change.

Effects on laboratory tests

Oral contraceptives may interfere with some laboratory estimations, in particular hormones, glucose tolerance, thyroid function, blood coagulation, serum triglycerides and liver function tests.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

None.

IDENTIFICATION

21 small beige coated tablets, and 7 large white coated non-hormonal tablets.

PRESENTATION

Calendar packs each containing 28 tablets

STORAGE INSTRUCTIONS

In original packs at room temperature (below 30°C). Protect from light. Keep out of reach of children. For shelf-life refer to the imprint on the pack.

REGISTRATION NUMBER

29/21.8.2/0685

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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