REGISTERED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

CLIMEN

Tablets

COMPOSITION

11 white tablets each containing estradiol-17-valerate (estra-1,3,5(10)-triene-3,17β-diol-17-valerate) 2 mg, plus
10 pink tablets each containing estradiol-17-valerate 2 mg and cyproterone acetate (6-chloro-17-hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione-acetate) 1 mg, plus
7 non-hormonal tablets.

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.2 Progesterones with estrogens.

PHARMACOLOGICAL ACTION

Estradiol valerate and cyproterone acetate are completely absorbed after oral administration. During the absorption process and the first liver passage, estradiol valerate but not cyproterone acetate is extensively metabolised. Despite complete absorption and ester hydrolysis of estradiol valerate only 3% of the dose is bioavailable as estradiol after oral administration. Cyproterone acetate is completely bioavailable after oral administration.

During the absorption process and the first liver passage estradiol valerate is rapidly hydrolysed to 17β-estradiol and valeric acid.

Cyproterone acetate is mainly metabolised to 15β-OH cyproterone acetate, a pharmacologically active metabolite with similar high antiandrogenic but much lower progestogenic activity as compared to the parent drug.

INDICATIONS

Climen is indicated in patients (with intact uteri) suffering from climacteric symptomatology.

Climen therapy may be used as an adjunct in preventing osteoporosis in postmenopausal women.

CONTRA-INDICATIONS

Pregnancy, lactation, severe disturbances of liver function, jaundice or persistent itching during a previous pregnancy, previous or existing tumours of the liver, uterus, ovaries or breast or a suspicion of such tumours, endometriosis, existing or previous thromboembolic processes, severe diabetes mellitus with vascular changes, sickle-cell anaemia, disturbances of lipometabolism, a history of herpes of pregnancy,

otosclerosis with deterioration during pregnancy.

WARNINGS

Climen is not a hormonal oral contraceptive preparation.

Strict medical supervision is necessary in patients with diabetes, hypertension, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, epilepsy, porphyria, tetany, chorea minor.

Reasons for immediate discontinuation of Climen

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, a feeling of pain and tightness in the chest, pending operations (six weeks beforehand), immobilisation, onset of jaundice, onset of hepatitis, itching of the whole body, increase in epileptic seizures, significant rise in blood pressure, pregnancy.

DOSAGE AND DIRECTIONS FOR USE

Before Climen is used, a thorough general medical (including measurement of blood pressure, analysis of urine for sugar, if applicable performance of special liver diagnostics as well) and gynaecological (including the breast and a cytological smear of the cervix and portio) examination should be performed in order to detect any diseases requiring treatment or risk factors and, where applicable, to rule out pregnancy. During the use, checks are recommended at intervals of about 6 months.

The pack contains seven self-adhesive strips marked with the days of the week. Each strip starts with a different day of the week. Stick the strip that starts with your "Start" day along the top of the memo-pack where indicated. For example, if the tablets are started on a Wednesday, the strip that starts with "Wed" should be selected. Each tablet is thus marked with the corresponding day of the week and one can see at a glance whether the tablet for that day has been taken or not.

Tablet-taking is always started from the blister marked "Start" and continued daily in the direction of the arrows until all 28 tablets have been taken. At the start of therapy the first tablet is taken on day 5 of the cycle (1st day of menstruation = 1st day of cycle). Menstruation will usually take place whilst the 7 non-hormonal tablets are being taken, before the next pack is started. The tablets are to be swallowed whole with some liquid.

Patients with amenorrhoea (rule out pregnancy beforehand) and postmenopausal women can start taking the tablets - 1 per day over 28 days - on any day they like.

After the 1st pack has been finished, the next pack of Climen is started on the following day.

If no withdrawal bleeding occurs whilst taking the 7 non-hormonal tablets at the end of the pack, tablet-taking from the new pack should not be commenced until pregnancy has been ruled out.

If a tablet is not taken at the usual time, it should be taken within 12 hours of that time in order to avoid the occurrence of intermenstrual bleeding.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

No toxicity studies involving repeated application of the combination of estradiol valerate and cyproterone acetate have been carried out.

Reproduction-toxicological investigations with the combination of the two active substances have not been carried out.

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 Climen.

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.

A feeling of tension in the breasts, intermenstrual bleeding, gastric complaints, nausea and changes of body weight and libido occur. Oedema, headache and depressive moods occur.

The frequency with which bleeding fails to occur in the tablet-free interval increases as the duration of treatment increases. If there is a chance that pregnancy has occurred, tablet-taking must be interrupted until it has been ruled out.

The repeated occurrence of intermenstrual bleeding in women undergoing replacement therapy must be clarified by diagnostic measures.

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 Climen. If severe upper abdominal complaints, liver enlargement or signs of intraabdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic reflections.

Interactions with other medicines

Various substances (eg barbiturates, phenylbutazone, hydantoins, rifampicin) accelerate the metabolism of steroid hormones (possible impairment of effect); reduced substance levels have also been observed on concurrent use of some antibiotics (eg ampicillin) as a result of alteration of the intestinal flora.

The requirement for antidiabetics or insulin can change as a result of an effect on glucose tolerance.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

None reported to date. See "Side-effects and special precautions". Treatment is symptomatic and supportive.

IDENTIFICATION

11 white, 10 pink and 7 non-hormonal lustrous coated tablets.

PRESENTATION

Calendar packs containing 1 x 28 tablets or 3 x 28 tablets.

STORAGE INSTRUCTIONS

In original packs at room temperature (below 30°C). Keep out of reach of children.

REGISTRATION NUMBER

Y/21.8.2/275

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

Bayer (Pty) Ltd
(Reg No: 1968/011192/07)
27 Wrench Road
ISANDO
1609

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