REGISTERED PACKAGE INSERT

SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

TRIODENE ED

Tablets

COMPOSITION

The 28-day pack (Every-Day pack) contains 21 hormonal tablets, 6 tablets each with gestodene (17α-ethinyl-13-ethyl-17β-hydroxy-4,15-gonadiene-3-one) 0,05 mg and ethinylestradiol (17α-ethinyl-estra-1,3,5(10)-triene-3,17β-diol) 0,03 mg, plus 5 tablets each with gestodene 0,07 mg and ethinylestradiol 0,04 mg, plus 10 tablets each with gestodene 0,10 mg and ethinylestradiol 0,03 mg, plus 7 non-hormonal tablets.

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.2 Progesterones with estrogens.

PHARMACOLOGICAL ACTION

Triodene ED is a low dose triphasic oral contraceptive which is well balanced in terms of estrogenic and progestogenic peripheral effects.

Triodene ED contains the progestogen gestodene, the biochemical profile of which is very similar to that of progesterone, in respect of binding sites for steroid hormones. With gestodene there is a virtual absence of estrogenic activity. The mode of action of gestodene in combination with ethinylestradiol includes the inhibition of ovulation by suppression of the mid-cycle surge of luteinising hormone, suppression of endometrial development thus rendering the endometrium unreceptive to implantation and the thickening of cervical mucus so as to constitute a barrier to sperm.

Pharmacokinetics

Ethinylestradiol and gestodene are rapidly and completely absorbed from the gastrointestinal tract. Peak plasma levels of each substance are reached within 1 to 2 hours. Post maximum concentration curves show two phases with half-lives of 1 and 15 hours in the case of gestodene, and 1 to 3 and approximately 24 hours in the case of ethinylestradiol. After oral administration, gestodene unlike ethinylestradiol is not subject to first-pass metabolism. Following oral administration, gestodene is completely bioavailable, ethinylestradiol about 40%.

Gestodene is extensively plasma protein bound to sex hormone binding globulin (SHBG). Ethinylestradiol is bound in plasma to albumin and enhances the binding capacity of SHBG. The elimination half-life for ethinylestradiol is approximately 25 hours. It is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present both free and as conjugates with glucuronide and sulphate. Conjugated ethinylestradiol is excreted in bile and is subject to enterohepatic recirculation. About 40% of the drug is excreted in the urine and 60% is eliminated in the faeces. The elimination half-life for gestodene is approximately 16 to 18 hours after multiple oral doses.

The substance is primarily metabolised by reduction of the A ring, followed by glucuronidation. About 60% of gestodene is excreted in the urine and 40% is eliminated in the faeces.

INDICATIONS

Oral contraception and the recognised gynaecological indications for such estrogen-progestogen combinations.

CONTRA-INDICATIONS

Pregnancy, severe disturbances of liver function, jaundice or persistent itching during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome, hormone dependent neoplasms, previous or existing liver tumours, existing or treated cancer of the breast or the endometrium, 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), sickle-cell anaemia, severe diabetes with vascular changes, disturbances of lipometabolism, a history of herpes of pregnancy, otosclerosis with deterioration during pregnancy.

Lactation, severe migraine or cerebrovascular insufficiency, recurrent cholestatic jaundice and undiagnosed vaginal bleeding.

Relative contra-indications include a history of diabetes mellitus, epilepsy, asthma, hypertension, depression, porphyria or states in which fluid retention occurs.

Reasons for immediate discontinuation of Triodene ED

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, increase in epileptic seizures, significant rise in blood pressure, pregnancy.

DOSAGE AND DIRECTIONS FOR USE

Before starting Triodene ED, a thorough general medical and gynaecological examination (including the breasts) 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.

Periodic medical examinations are advisable during long-term treatment.

Initial course

The first course of Triodene ED is started on the first day of the menstrual period (day 1 of the cycle) from the silver section of the pack by selecting the appropriate tablet for that day of the week (eg "Mon" for Monday). The tablet is swallowed whole with some liquid. Thereafter one tablet must be taken every day following the direction shown by the arrows. 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.

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 silver section of the calendar pack marked with the appropriate day of the week.

When taken according to instructions, a menstruation-like bleeding is induced at regular intervals of approximately 28 days.

Normally, a bleeding will occur while the tablets from the silver section of the packs are being taken. If, in exceptional cases, bleeding fails to occur while the tablets from the silver section are being taken, tablet-taking must provisionally be stopped and the doctor must be consulted.

If the patient starts Triodene ED during the latter part of the week, the very first cycle may be slightly shortened.

After delivery or abortion, or when switching from other hormonal contraceptives, the patient must follow the doctor's instructions.

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.

If the patient forgets to take a Triodene ED 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, the contraceptive protection in this cycle may be reduced. She must nevertheless continue to take the other tablets in the pack at the usual time, forgetting about the ones she has missed. At the same time, however, an additional, non-hormonal method of contraception (with the exception of the rhythm and temperature methods) must be employed until bleeding occurs. The tablet or tablets which she missed should not be taken at all.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

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.

Prolonged amenorrhoea following the use of oral contraceptives may occur. The incidence is not higher than in non-users. Caution is advised where oligomenorrhoea or amenorrhoea have occurred in the past.

Side-effects such as nausea, vomiting, headaches, mood changes, breast tension, skin pigmentation, vaginal candidiasis, gall-bladder disease, gastro-intestinal irritation, poor tolerance of contact lenses, fluid retention, changes in libido, weight gain and hypertension may occur. Regular blood pressure checks, including a pretreatment level, are advisable.

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 Triodene ED. 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 tablets be stopped without having adopted a satisfactory alternative method of contraception.

Triodene ED may only be taken under strict medical supervision in the case of diabetes or a tendency thereto, high blood pressure, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, epilepsy, porphyria, tetany, chorea minor.

Intermenstrual bleeding, ie while the small white tablets are being taken, is more likely to occur during the first few cycles of use. If intermenstrual bleeding occurs, pill-taking should not be interrupted as a slight bleeding will usually stop spontaneously. However, if the bleeding is heavy, similar to menstrual bleeding, then a thorough examination is indicated to exclude organic factors.

Interaction with other medicines and efficacy

The efficacy of the contraceptive pill may be decreased when it is administered concomitantly with other medicines such as the anti-epileptic agents, ampicillin, barbiturates and rifampicin, and in patients with very rare individual metabolic disturbances.

The requirement for oral antidiabetics or insulin can change.

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. 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.

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

Symptomatic treatment according to conventional methods.

IDENTIFICATION

6 small beige coated hormonal tablets, 5 small dark brown coated hormonal tablets, 10 small white coated hormonal tablets, and 7 large white coated non-hormonal tablets.

PRESENTATION

Cartons with one or three 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

W/21.8.2/317

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

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