REGISTERED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

ANDROCUR 10 mg

Tablets
Oral antiandrogen

COMPOSITION

1 Androcur 10 mg tablet contains cyproterone acetate (6-chloro-17-hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione-acetate) 10 mg.

PHARMACOLOGICAL CLASSIFICATION

A. 21.12 Hormone inhibitors.

PHARMACOLOGICAL ACTION

Androcur is an antiandrogenic hormone preparation.
The active substance, cyproterone acetate, has three partial effects:
an antiandrogenic effect, a progestational effect and an antigonadotropic effect.
Cyproterone acetate 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.
The inherent progestational activity exerts a negative feedback on the hypothalamic receptors so leading to a reduction in gonadotropin release, and hence to diminished production of androgens.

INDICATIONS

Moderately severe signs of androgenisation in women, eg:

- moderately severe forms of hirsutism.
- moderately severe androgen-dependent loss of scalp hair (moderately severe androgenetic alopecia).
- severe and moderately severe forms of acne and seborrhoea.

CONTRA-INDICATIONS

Pregnancy; lactation; liver diseases; a history of jaundice or persistent itching during a previous pregnancy; a history of herpes of pregnancy; Dubin-Johnson syndrome; Rotor syndrome; previous or existing liver tumours; wasting diseases; depression; previous or existing thromboembolic processes; diabetes with vascular changes; sickle-cell anaemia.

DOSAGE AND DIRECTIONS FOR USE

Before starting Androcur therapy a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out. Since pregnant women must not take Androcur, pregnancy must be excluded.

For the duration of Androcur therapy women of child-bearing age must also receive a combination oral contraceptive. This will provide the necessary contraceptive protection and will stabilise the menstrual cycle. Dosage and directions for use as per the package insert of that product should be strictly adhered to.

Prior to commencing Androcur treatment it is always necessary for the patient to receive one complete cycle of a combination oral contraceptive.

Extra non-hormonal methods (with the exception of the rhythm and temperature methods) should be employed during the first 3 weeks of the first cycle, which may be shorter than 4 weeks. Subsequent cycles should then be regular.

In the subsequent cycle of the combination oral contraceptive (second cycle) which starts the very next day after completion of the first pack of combination oral contraceptive, Androcur treatment is commenced on the 5th day of the menstrual cycle (1st day of bleeding = 1st day of the menstrual cycle) regardless of whether bleeding has stopped or not, ie 5th to 19th day of cycle inclusive.

The first Androcur 10 mg tablet is taken from the memo-pack out of one of the blisters marked with the corresponding day of the week (for example "Mon" for Monday) and swallowed whole with some liquid. It does not matter at what time of the day the patient takes the tablet, but once she has selected a particular time - preferably after her breakfast or evening meal - she should keep to it.

From now on the patient must take a tablet every day in the direction indicated by the arrows on the pack (altogether 14 tablets) and as the last tablet of the Androcur treatment, the one from the section marked with number "15".

Every 28 days (the usual duration of a menstrual cycle), the above dosage regimen is to be followed.

Women receiving the cyclical combined Androcur and combination oral contraceptive therapy, should keep to a particular time of the day for tablet taking. If more than 12 hours elapse from this time contraceptive protection in this cycle may be reduced. The use of these two products should nevertheless be continued according to instructions, ignoring the missed tablet or tablets, in order to avoid premature bleeding in this cycle. However, an additional non-hormonal method of contraception (with the exception of the rhythm and temperature methods) is to be employed for the rest of the cycle.

If bleeding fails to occur during the last days of the 28-day cycle, the doctor must be consulted.

The length of treatment is determined by the severity of the pathological signs of androgenisation and their response to treatment. Treatment may have to last several months. Acne and seborrhoea usually respond sooner than hirsutism or alopecia.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Administration of high doses of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (starting roughly on day 45 of gravidity) could cause feminisation effects in male foetuses. Observation of male newborn children who had been exposed in the uterus to cyproterone acetate revealed no indications of feminisation. However, pregnancy is a contra-indication for the use of Androcur. Women of child-bearing age should only be treated if reliable contraceptive measures are taken at the same time.

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 can promote the growth of certain hormone-dependent tissues and tumours.

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 sex steroids to which the substance contained in Androcur 10 mg also belongs. If severe upper abdominal complaints, liver enlargement or signs of intraabdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

Changes in body-weight and libido, a feeling of tension in the breasts, tiredness, diminished vitality, inner restlessness and depressive moods may occur.

Attention is drawn to the special notes on side-effects, reasons for immediate discontinuation of treatment as well as all relevant data contained in the package insert of the combination oral contraceptive preparation.

Disturbances of liver function, acute and fulminant hepatitis have been reported with high-dose Androcur treatment. During treatment, liver function should be checked regularly.

In diabetics, carbohydrate metabolism should also be monitored particularly carefully.

Before the start of therapy, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out. Pregnancy must be excluded in women of child-bearing age.

Ovulation is inhibited under the combined cyclical treatment, so that a state of infertility exists. This is essential because if Androcur were taken during pregnancy, the properties of the preparation could lead to signs of feminisation in male neonates.

A high-dosed treatment may reduce the function of the adrenal cortex, particularly the adrenocortical response to stress.

If, during the combined cyclical treatment, slight "unscheduled" bleeding occurs, tablet-taking should not be interrupted. However, if the bleeding is heavy, the patient should consult her doctor.

It should be pointed out to patients whose occupation demands great concentration (eg road users and machine operators) that Androcur can lead to tiredness and diminished vitality and can impair the ability to concentrate.

Androcur 10 mg should not be given before the conclusion of puberty since an unfavourable influence on the longitudinal growth and the still unstabilised axes of endocrine function cannot be ruled out.

Androcur should be used with caution in cardiovascular disease, ischemic heart disease, cerebrovascular disease and hypertension.

Haemoglobin and red cell counts may decrease on therapy with Androcur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See side-effects. Treatment is supportive and symptomatic.

IDENTIFICATION

White to faintly yellowish, round, flat-sided tablets with bevelled edges, scored on the one side.

PRESENTATION

Memo-packs of 15 tablets.

STORAGE INSTRUCTIONS

Store below 30°C. Keep out of reach of children.

REGISTRATION NUMBER

R/21.12/159

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