**SCHEDULING STATUS** S4

**PROPRIETARY NAME AND DOSAGE FORM**

# ANDROCUR DEPOT

Solution for injection

**COMPOSITION**

One 3 ml ampoule Androcur Depot contains cyproterone acetate (6-chloro-17-hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione-acetate) 300 mg in oily solution.

**PHARMACOLOGICAL CLASSIFICATION**

A. 21.12 Hormone inhibitors.

**PHARMACOLOGICAL ACTION**

**Pharmacodynamic properties**

Cyproterone acetate has antiandrogenic, progestational and antigonadotropic effects.

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.

Cyproterone acetate has a central inhibiting effect. The antigonadotropic effect leads to a reduction of testosterone synthesis in the testes and, hence, to a reduction of the serum concentration of testosterone.

Cyproterone acetate inhibits competitively the effect of androgens at androgen-dependent target organs.

In males, under treatment with cyproterone acetate, sexual drive and potency are reduced and gonadal function is inhibited. These changes are reversible following discontinuation of the therapy.

The antigonadotropic effect of cyproterone acetate is also exerted when the substance is combined with GnRH agonists. The initial increase of testosterone provoked by this substance group is decreased by cyproterone acetate.

**Pharmacokinetic properties**

After intramuscular administration, cyproterone acetate was released slowly and completely from the intramuscular depot. Maximum drug levels in the serum of 180 ± 54 ng/ml were achieved after about 2 to 3 days. Thereafter, drug serum levels declined with a terminal half-life of 4 ± 1,1 days. The total clearance of cyproterone acetate from serum was determined to be 2,8 ± 1,4 ml/min/kg. Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15β-hydroxy derivative. Phase I metabolism of cyproterone acetate is mainly catalysed by the cytochrome P450 enzyme CYP3A4.

Cyproterone acetate is partly excreted unchanged with bile fluid. Most of the dose is excreted in form of metabolites with urine and faeces.

Cyproterone acetate is about 96 % plasma protein bound, almost exclusively to plasma albumin. Because protein binding is non-specific, changes in sex hormone binding globulin (SHBG) levels do not affect the pharmacokinetics of cyproterone acetate.

According to the long half-life of the terminal disposition phase from plasma (serum) and the dosing interval of 7 days, an accumulation of cyproterone acetate can be expected in the serum during repeated administration. An equilibrium between the release of the drug from the depot and the elimination can be expected after about 5 weeks.

The absolute bioavailability of cyproterone acetate after IM injection can be assumed to be complete.

**Preclinical safety data**

*Genotoxicity and carcinogenicity*

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, 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 systemic exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. *In vivo* consequences of cyproterone acetate treatment were the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats, and an increase of mutation frequency in transgenic rats carrying a bacterial gene as target for mutations.

Clinical experience and well conducted epidemiological trials 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.

Experimental investigations produced corticoid-like effects on the adrenal glands in rats and dogs following higher dosages, which could indicate similar effects in humans at the highest given dose (300 mg/day).

## INDICATIONS

Reduction of drive in sexual deviations in males; inoperable carcinoma of the prostate.

## CONTRA-INDICATIONS

- Liver diseases.
- Dubin-Johnson syndrome, Rotor syndrome.

- Previous or existing liver tumours (only if these are not due to metastases from carcinoma of the prostate).
- Wasting diseases (with the exception of inoperable carcinoma of the prostate).
- Depression.
- Previous or existing thromboembolic processes.
- Severe diabetes with vascular changes.
- Sickle-cell anaemia.
- Hypersensitivity to any of the components of Androcur Depot.

**WARNINGS**

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

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200 to 300 mg Androcur. Most reported cases are in males with carcinoma of the prostate. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, Androcur should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case Androcur should be continued only if the perceived benefit outweighs the risk.

In rare cases benign, and in even rarer cases malignant, liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of sex steroids to which the substance contained in Androcur Depot also belongs. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

A sensation of shortness of breath may occur in individual cases under high-dosed treatment with Androcur Depot. The differential diagnosis in such cases must include the stimulating effect on breathing known for progesterone and synthetic progestogens which is accompanied by hypocapnia and compensatory respiratory alkalosis and which is not considered to require treatment.

The occurrence of thromboembolic events has been reported in patients using Androcur Depot, although a causal relationship has not been established. Patients with previous arterial or venous thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, and myocardial infarction) or with a history of cerebrovascular accidents or with advanced malignancies are at increased risk of further thromboembolic events.

In patients with inoperable carcinoma of the prostate, presenting with a history of thromboembolic processes or suffering from sickle-cell anaemia or from severe diabetes with vascular changes, a careful risk:benefit evaluation must be carried out in each individual case before Androcur is prescribed.

Prolactin levels may increase with higher doses of Androcur.

**INTERACTIONS**

The requirement for oral antidiabetics or insulin can change.

Although clinical interaction studies have not been performed it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4 will inhibit the metabolism of Androcur as it is metabolised by CYP3A4. On the other hand, inducers of CYP3A4 such as e.g. rifampicin, phenytoin and products containing St John's Wort may reduce the levels of Androcur.

Based on *in vitro* inhibition studies, an inhibition of the cytochrome P450 enzymes CYP2C8, 2C9, 2C19, 3A4 and 2D6 is possible at high therapeutic Androcur doses of 3 times 100 mg per day.

The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMGCoA inhibitors (statins), which are primarily metabolised by CYP3A4, are coadministered with high therapeutic Androcur doses since they share the same metabolic pathway.

**PREGNANCY AND LACTATION**

Not applicable.

## DOSAGE AND DIRECTIONS FOR USE

The injections must be administered very slowly. Androcur Depot is strictly for intramuscular injection. Special care must be given to avoid intravasal injection.

**Reduction of drive in sexual deviations in males**

In general, 1 ampoule of Androcur Depot is given as a deep intramuscular injection every 10 to 21 days. If, in exceptional cases, the effect is inadequate, 2 ampoules can be given every 10 to 21 days, preferably as 1 ampoule each in the right and left gluteal muscles. Efficacy can be maintained by injection intervals ranging from 10 to 21 days.

When the therapeutic result is considered to be satisfactory, an attempt should be made to reduce the dosage by gradually increasing the intervals between injections.

To stabilise the therapeutic effect it is necessary to administer Androcur Depot over a protracted period of time, if possible with the simultaneous use of psychotherapeutic measures.

**Inoperable carcinoma of the prostate**

*After orchidectomy:*

300 mg (1 ampoule) every 2 weeks as a deep IM injection.

*Without orchidectomy:*

300 mg (1 ampoule) weekly as a deep IM injection.

Treatment should not be interrupted nor the dosage reduced after improvement or remissions have occurred.

## SIDE EFFECTS AND SPECIAL PRECAUTIONS

| System Organ Class MedDRA v 8.0 | Very common ≥ 1/10 | Common ≥ 1/100 and < 1/10 | Uncommon ≥ 1/1000 and < 1/100 | Rare ≥ 1/10 000 and < 1/1000 | Very rare < 1/10 000 |
|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | | | Thromboembolic events | Changes in the number of red blood cells |
| Immune system disorders | | | | Hypersensitivity reaction | |
| Endocrine disorders | | | | | Reduction of adrenocortical function<br>Increase in prolactin levels |

| | | | | | |
|---|---|---|---|---|---|
| Metabolism and nutrition disorders | | Weight increased or weight decreased | | | |
| Psychiatric disorders | Libido decreased<br>Erectile dysfunction | Depressed mood<br>Restlessness (temporary) | | | |
| Respiratory, thoracic and mediastinal disorders | | Shortness of breath | | | |
| Hepato-biliary disorders | | Hepatic toxicity including jaundice, abnormal liver function tests, and toxic hepatitis | | | |
| Skin and subcutaneous tissue disorders | | | Rash | | |
| Musculoskeletal and connective tissue disorders | | | | | Osteoporosis |
| Reproductive system and breast disorders | Reversible inhibition of spermatogenesis | Gynaecomastia<br>Feeling of tension in the breasts | | | |
| General disorders and administration site conditions | | Fatigue<br>Hot flushes<br>Sweating | | | |

Under treatment with Androcur Depot, sexual drive and potency are reduced and gonadal function is inhibited. These changes are reversible after discontinuation of therapy.

Over the course of several weeks, Androcur Depot inhibits spermatogenesis as a result of the antiandrogenic and antigonadotropic actions. Spermatogenesis recovers gradually within a few months of discontinuing the therapy.

Androcur Depot may lead to gynaecomastia (sometimes combined with tenderness to touch of the mamillae) which usually regresses after withdrawal of the preparation. Permanent enlargement of the mammary glands may occur. Galactorrhoea and benign nodules have been reported.

Long-term androgen deprivation with Androcur may lead to osteoporosis.

**Special Precautions**

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

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

During treatment, liver function, adrenocortical function and the red blood-cell count should be checked regularly.

Strict medical supervision is necessary if the patient suffers from diabetes.

In the indication “reduction of drive in sexual deviations”, the drive-reducing effect of Androcur Depot can be diminished under the disinhibitory influence of alcohol.

As Androcur Depot is an oily solution, it must be injected intramuscularly. Experience shows that the short-lasting reactions (urge to cough, coughing fits, respiratory distress) which occur in rare cases during or immediately after the injection of Androcur Depot can be avoided by injecting the solution extremely slowly.

*Effects on ability to drive and use machines*

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

## KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See “Side effects and Special Precautions”. Treatment is supportive and symptomatic.

## IDENTIFICATION

Clear, colourless to faintly yellowish oily solution in 3 ml amber glass ampoules.

## PRESENTATION

Amber glass ampoules of 3 ml.

## STORAGE INSTRUCTIONS

Protect from light. Store below 30 °C. Keep out of reach of children.

**REGISTRATION NUMBER**

R/21.12/184

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

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