

**SCHEDULING STATUS**

**S4**

**PROPRIETARY NAME AND DOSAGE FORM**

**ANDROCUR 50 mg**

**ANDROCUR 100 mg**

Tablets

**COMPOSITION**

**Androcur 50 mg** tablets: 1 Androcur 50 mg tablet contains cyproterone acetate (6-chloro-17-hydroxy-1 $\alpha$ ,2 $\alpha$ -methylene-pregna-4,6-diene-3,20-dione-acetate) 50 mg.

**Androcur 100 mg** tablets: 1 Androcur 100 mg tablet contains cyproterone acetate (6-chloro-17-hydroxy-1 $\alpha$ ,2 $\alpha$ -methylene-pregna-4,6-diene-3,20-dione-acetate) 100 mg.

**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, 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**

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range.

The ingestion of 50 mg of cyproterone acetate gives maximum serum levels of about 140 ng /ml at about 3 hours. Thereafter, drug serum levels declined during a time interval of typically 24 to 120 hours, with a terminal half-life of  $43,9 \pm 12,8$  hours. The total clearance of cyproterone acetate from serum was determined to be  $3,5 \pm 1,5$  ml/ min/ kg.

The ingestion of 100 mg of cyproterone acetate gives maximum serum levels of  $239,2 \pm 114,2$  ng/ ml at  $2,8 \pm 1,1$  hours. Thereafter, drug serum levels declined during a time interval of typically 24 to 120 hours, with a terminal half-life of  $42,8 \pm 9,7$  hours. The total clearance of cyproterone acetate from serum was determined to be  $3,8 \pm 2,2$  ml/ min/ kg.

Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the  $15\beta$ -hydroxy derivative. Phase I metabolism of cyproterone acetate is mainly catalysed by the cytochrome P450 enzyme CYP3A4.

Cyproterone is partly excreted unchanged with bile fluid. Most of the dose is excreted in form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with a half-life of 1,9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1,7 days).

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 daily intake, an accumulation of cyproterone acetate by a factor of about 3 can be expected in the serum during repeated daily administration.

The absolute bioavailability of cyproterone acetate is almost complete (88 % of dose).

**Preclinical safety data***Embryotoxicity/ teratogenicity*

Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs led 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 cyproterone (See Pregnancy and lactation).

*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**

**Androcur 50 mg tablets:**

### ***Indications in females***

Severe signs of androgenisation, e.g. very severe hirsutism, androgen-dependent severe loss of scalp hair eventually resulting in baldness (severe androgenic alopecia), often attended by severe forms of acne and/ or seborrhoea.

### ***Indications in males***

Suppress drives in sexual deviants.

Anti-androgen treatment in inoperable carcinoma of the prostate.

**Androcur 100 mg tablets:**

Inoperable carcinoma of the prostate.

## **CONTRA-INDICATIONS**

### **Contra-indications in females**

- Pregnancy.
- Lactation.
- Liver diseases.

- Dubin-Johnson syndrome, Rotor syndrome.
- History of jaundice or persistent pruritus during a previous pregnancy.
- History of herpes of pregnancy.
- Previous or existing liver tumours.
- Wasting diseases.
- Severe chronic depression.
- Previous or existing thromboembolic processes.
- Severe diabetes with vascular changes.
- Sickle-cell anaemia.
- Hypersensitivity to any of the components of Androcur 50 mg.

With regard to the cyclical combined therapy of severe signs of androgenisation, attention is also drawn to the data on contra-indications contained in the package insert for the product used in addition to Androcur 50 mg.

**Contra-indications in males**

- 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).
- Severe chronic depression.
- Previous or existing thromboembolic processes.
- Severe diabetes with vascular changes.
- Sickle-cell anaemia.
- Hypersensitivity to any of the components of Androcur.

**WARNINGS**

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.

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 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. 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 compensated respiratory alkalosis and which is not considered to require treatment.

The occurrence of thromboembolic events has been reported in patients using Androcur, although a causal relationship has not been established. Patients with previous arterial or venous thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, 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 co-administered with high therapeutic Androcur doses since they share the same metabolic pathway.

**PREGNANCY AND LACTATION**

The administration of Androcur during pregnancy and lactation is contra-indicated (See Contra-Indications).

In a study with 6 women who received a single oral dose of 50 mg Androcur, 0,2 % of the dose was excreted with breast milk.

**DOSAGE AND DIRECTIONS FOR USE****Dosage in females****For severe signs of androgenisation***Women of child-bearing age*

Pregnant women must not take Androcur 50 mg. Therefore pregnancy must be excluded before the start of therapy (See Contra-indications).

For the duration of Androcur therapy women of child-bearing age must also receive a combined 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 must be strictly adhered to.

Prior to commencing Androcur treatment it is always necessary for the patient to receive one complete cycle of a combined 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 pack of the combined oral contraceptive. This menstrual cycle may be shorter than 4 weeks. Subsequent cycles should then be regular.

In the second pack of the combined oral contraceptive, which starts the very next day after completion of the first pack of the combined oral contraceptive, Androcur treatment is commenced on the 5th day of this menstrual cycle (1st day of bleeding = 1st day of the menstrual cycle).

2 Androcur 50 mg tablets (= 100 mg) are to be taken with some liquid after a meal from the 5th to the 14th day of the cycle (i.e. for ten days).

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

Women receiving the cyclical combined therapy should keep to a particular time of the day for tablet-taking.

Seven inactive tablets are taken once daily after 21 days, during which time a withdrawal bleeding occurs. Exactly 4 weeks after the first course of treatment was started, i.e. on the same day of the week, the next cyclical course of combined treatment is started, regardless of whether bleeding has stopped or not.

Following clinical improvement, the daily dose of Androcur 50 mg during the 10 days of the combined treatment with a combined oral contraceptive can be reduced to one or half a tablet of Androcur 50 mg.



*Missed bleeding*

If no bleeding occurs during the inactive tablet phase, the treatment must be interrupted and pregnancy must be excluded before tablet-taking is resumed.

*Missed tablets*

Women receiving the cyclical combined therapy should keep to a particular time of the day for tablet taking. If more than 12 hours elapse from the time that she normally takes her combined oral contraceptive, contraceptive protection may be reduced in this cycle. Attention is drawn to the special notes (especially on contraceptive reliability and to the missed tablet recommendations) in the package insert for the combined oral contraceptive. If bleeding fails to occur after this cycle, pregnancy must be excluded before tablet-taking is resumed.

Missed Androcur 50 mg tablets may diminish the therapeutic efficacy and may lead to intermenstrual bleeding. The missed Androcur 50 mg tablet should be disregarded (no double dose should be taken to make up for the missed tablet) and tablet-taking resumed at the regular time together with the combined oral contraceptive.

*Post-menopausal or hysterectomised patients*

In postmenopausal or hysterectomised patients Androcur 50 mg may be administered alone. According to the severity of the complaints, the average dose should be one to half a tablet Androcur 50 mg once daily for 21 days, followed by a seven day tablet-free interval.

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

The tablets are to be taken with some liquid after meals. Generally treatment is started with one tablet Androcur 50 mg twice daily. It may be necessary to increase the dose to two tablets twice daily, or even two tablets three times daily for a short period of time. When a satisfactory result has been achieved, one should try to maintain the therapeutic effect with the lowest possible dose. Quite often half a 50 mg tablet twice daily (50 mg daily) is sufficient. When establishing the maintenance dose or when discontinuing the preparation, dosage should not be reduced abruptly, but gradually. To this end, the daily dose should be reduced by one 50 mg tablet, or better  $\frac{1}{2}$  of a 50 mg tablet, at intervals of several weeks.

To stabilise the therapeutic effect it is necessary to take Androcur 50 mg over a protracted period of time, if possible with the simultaneous use of psychotherapeutic measures.

### **Antiandrogen treatment in inoperable carcinoma of the prostate**

100 mg twice to three times daily (= 200-300 mg per day).

The tablets are to be taken with some liquid after meals.

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

### **To reduce the initial increase of male sex hormones in treatment with GnRH agonists**

100 mg twice daily (= 200 mg per day) alone for 5-7 days, followed by 100 mg twice daily (= 200 mg per day) for 3-4 weeks together with a GnRH agonist in the dosage recommended by the manufacturer.

### **To treat hot flushes in patients under treatment with GnRH analogues or who have had orchidectomy**

100 mg once to twice daily (= 100-200 mg per day).

## **SIDE EFFECTS AND SPECIAL PRECAUTIONS**

### **Side effects**

<b>System Organ Class MedDRA v 8.0</b>	<b>Very common ≥ 1/10</b>	<b>Common ≥ 1/100 and &lt; 1/10</b>	<b>Uncommon ≥ 1/1000 and &lt; 1/100</b>	<b>Rare ≥ 1/10 000 and &lt; 1/1000</b>	<b>Very rare &lt; 1/10 000</b>
Blood and lymphatic system disorders				Thromboembolic events	Changes in the number of red cells
Immune system disorders				Hypersensitivity reaction	
Endocrine disorders					Reduction of adrenocortical function Increase in prolactin levels
Metabolism and nutrition disorders		Weight increased or weight decreased			
Psychiatric disorders	Libido decreased (males) Erectile dysfunction (males)	Depressed mood Restlessness (temporary)	Libido decreased (women)	Libido increased (women)	
Respiratory, thoracic and mediastinal		Shortness of breath			

disorders					
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 (males)
Reproductive system and breast disorders	Ovulation inhibited (women) Reversible inhibition of spermatogenesis (males)	Breast tenderness (women) Gynaecomastia, breast tenderness (males)			
General disorders and administration site conditions		Fatigue Hot flushes (males) Sweating (males)			

In male patients, under treatment with Androcur, 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 inhibits spermatogenesis as a result of the antiandrogenic and antigonadotropic actions. Spermatogenesis recovers gradually within a few months of discontinuing the therapy.

In male patients, Androcur 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.

In male patients long-term androgen deprivation with Androcur may lead to osteoporosis.

In women, ovulation is inhibited under the combined treatment, so that a state of infertility exists.

### **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.

*Specifically to be observed in woman*

Before starting treatment, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out and pregnancy must be excluded.

If, during the combined treatment, spotting occurs during the 3 weeks in which the tablets are being taken, tablet-taking should not be interrupted. However, if persistent or recurrent bleeding occurs at irregular intervals, a gynaecological examination must be carried out to exclude organic disease.

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

*Specifically to be observed in males*

In the indication "reduction of drive in sexual deviations", the drive-reducing effect of Androcur 50 mg can be diminished under the disinhibitory influence of alcohol.

*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 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**

**Androcur 50 mg** tablets: White to faintly yellowish, round, flat-sided tablets with bevelled edges. Upper surface: imprinted with BV in an equilateral hexagon; lower surface: scored.

**Androcur 100 mg** tablets: White to faintly yellowish capsule-shaped tablets. Upper surface: imprinted with "LA" on both sides of the score; lower surface: imprinted with an equilateral hexagon.

**PRESENTATION**

**Androcur 50 mg** tablets: Cartons containing amber glass bottles of 20 or 50 tablets or 2 or 5 transparent PVC/aluminium blisters with 10 tablets per blister.

**Androcur 100 mg** tablets: Cartons containing 6 or 12 transparent PVC/aluminium blisters with 10 tablets per blister.

**STORAGE INSTRUCTIONS**

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

**REGISTRATION NUMBERS**

**Androcur 50 mg** tablets: R/21.12/160

**Androcur 100 mg** tablets: 29/21.12/0515

**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

**DATE OF PUBLICATION OF THE PACKAGE INSERT**

13 June 2009