SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Androcur 50 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg cyproterone acetate.

Excipient with known effect: lactose 108.75 mg.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round tablet, scored on one side and embossed with the letters “BV” in a regular hexagon on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Control of libido in severe hypersexuality and/or sexual deviation in the adult male.

For reduction of drive in sexual deviations in men, cyproterone acetate 50 mg can be used when other interventions are considered inappropriate.

4.2 Posology and method of administration

Posology

Adults
Generally, treatment is started with 1 tablet Androcur 50 mg twice daily, after the morning and evening meals. The duration of cyproterone acetate treatment should be defined on an individual basis. When a satisfactory result has been achieved, the therapeutic effect should be maintained with the lowest possible dose. When changing the dose or when discontinuing cyproterone acetate, this should be done gradually.

Additional information on special populations

Paediatric population
Androcur is not recommended for use in male children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Androcur must 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.

Older people
There are no data suggesting the need for a dosage adjustment in elderly patients.

Patients with hepatic impairment:
The use of Androcur is contraindicated in patients with liver diseases (see section 4.4 and 4.8).

Patients with renal impairment:
The use of Androcur in patients with renal impairment has not been investigated. There are no data suggesting the need for dosage adjustment in patients with renal impairment (see section 5.2).

Method of administration

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

4.3 Contraindications

Androcur must not be used in patients with:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Liver diseases (including Dubin-Johnson syndrome and Rotor syndrome)

Malignant tumours (except for carcinoma of the prostate)

Previous or existing liver tumours

Wasting diseases (because of transient catabolic action)

A history of or existing thrombosis or embolism

Severe diabetes with vascular changes

Sickle cell anaemia

Severe chronic depression

Meningioma or a history of meningioma.

Androcur should not be given to youths under 18 or to those whose bone maturation and testicular development are incomplete.

4.4 Special warnings and precautions for use

Liver: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, has been observed in patients treated with Androcur. At dosages of 100mg and above, cases with fatal outcome have also been reported. Most reported fatal cases were in men with advanced prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment, regularly during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, Androcur should 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 very rare cases benign and malignant liver tumours, which may lead to life-threatening intra-abdominal haemorrhage have been observed after the use of Androcur. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis.

Thromboembolic events: The occurrence of thromboembolic events has been reported patients using Androcur, although a causal relationship has not been established. Patients with previous arterial or venous thrombotic / thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infarction), with a history of cerebrovascular accidents or with

advanced malignancies are at increased risk of further thromboembolic events, and may be at risk of recurrence of the disease during Androcur therapy. See also section 4.3.

Meningiomas: The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate primarily at doses of 25 mg and above. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate (see section 5.1). High cumulative doses can be reached with prolonged use (several years) or shorter duration with high daily doses. Patients should be monitored for meningiomas in accordance with clinical practice. If a patient treated with Androcur is diagnosed with meningioma, treatment with Androcur and other cyproterone containing products must be
permanently stopped (see section 'Contraindications').
There is some evidence that the meningioma risk may decrease after treatment discontinuation of cyproterone.

Shortness of breaths: Shortness of breath may occur under high-dosed treatment with Androcur. This may be due to the stimulatory effect of progesterone and synthetic progestogens on breathing, which is accompanied by hypocapnia and compensatory alkalosis, and which is not considered to require treatment.

Adrenocortical function: During treatment adrenocortical function should be checked regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of Androcur with high doses (see section 5.3).

Diabetes mellitus: Strict medical supervision is necessary if the patient suffers from diabetes as Androcur can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment because the requirement for oral antidiabetics or insulin can change. See also section 4.5.

Anaemia: Anaemia has been reported during long-term treatment. Therefore, the red blood count should be checked regularly during treatment.

Lactose: Androcur contains 108.75 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Patients who are on a lactose-free diet should take this amount into consideration.

Spermatogenesis: A spermatogram should be recorded before starting treatment in patients of procreative age, as a guard against attribution of pre-existing infertility to Androcur at a later stage. It should be noted that the decline in spermatogenesis is slow, and Androcur should, therefore, not be regarded as a male contraceptive.

Medico-legal considerations: Doctors are advised to ensure that the fully informed consent of the patient to Androcur treatment is witnessed and can be verified.

4.5 Interaction with other medicinal products and other forms of interaction

Diabetes: At high therapeutic cyproterone acetate doses of three times 100mg per day, cyproterone acetate may inhibit CYP2C8 (see below). Thiazolidinediones (i.e. the anti-diabetics pioglitazone and rosiglitazone) are substrates or CYP2C8 (increased blood levels of these anti-diabetics may require dose adjustment).

Chronic alcoholism: Alcohol appears to reduce the effect of Androcur which is of no value in chronic alcoholics.

Other interactions: Clinical interaction studies have not been performed. However, since cyproterone acetate is metabolised by CYP3A4, it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4 inhibit the metabolism of cyproterone acetate. On the other hand, inducers of CYP3A4 such as rifampicin, phenytoin and products containing St. John's Wort may reduce the levels of cyproterone acetate.

Based on in vitro inhibition studies, an inhibition of the cytochrome P450 enzymes CYP2C8, 2C9, 2C19, 3A4 and 2D6 is possible at high cyproterone acetate doses of 100mg three times per day. (This is three times the maximum total daily dose).

The risk of *statin*-associated myopathy or rhabdomyolysis may be increased when those HMG-CoA inhibitors (statins) which are primarily metabolised by CYP3A4 are co-administered with high cyproterone acetate doses, since they share the same metabolic pathway.

4.6 Fertility, Pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Fatigue and lassitude are common - patients should be warned about this and if affected should not drive or operate machinery.

4.8 Undesirable effects

The most frequently observed adverse drug reactions (ADRs) in patients receiving Androcur are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious ADRs in patients receiving Androcur are hepatic toxicity, benign and malignant liver tumours which may lead to intra-abdominal haemorrhage and thromboembolic events.

The following approximate incidences were estimated from published reports of a number of small clinical trials and spontaneous ADR reports:

- very common: incidence ≥ 1:10
- common: incidence < 1:10 but ≥ 1:100
- uncommon: incidence < 1:100 but ≥ 1:1,000
- rare: incidence < 1:1,000 but ≥ 1:10,000
- very rare: incidence < 1:10,000
- not known (cannot be estimated from available data)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Rare:	Meningioma. The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate (see section 4.4).
Very rare:	Benign and malignant liver tumours which may lead to life-threatening intra abdominal haemorrhage (see section 4.4).

Blood and the lymphatic system disorders

Not known:	Anaemia during long-term treatment (see section 4.4).

Immune system disorders

Rare:	Hypersensitivity reactions may occur.

Endocrine disorders

Not known:	Suppression of adrenocorticol function.

Metabolism and nutrition disorders

Common:	Changes in bodyweight during long term treatment (chiefly weight gains in association with fluid retention)

Psychiatric disorders

Common:	Depressive moods and restlessness (temporary).

Vascular disorders

Not known: Thromboembolic events, although a causal relationship has not been established (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea (see section 4.4).

Hepato-biliary disorders
Common: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure has been observed in patients treated with Androcur. At dosages of 100 mg and above, cases with fatal outcome have also been reported. Most reported fatal cases were in men with advanced carcinoma of the prostate. Toxicity is dose related and develops, usually, several months after treatment has begun.

Skin and subcutaneous tissue disorders
Uncommon: Rash
Not known: Reduction of sebum production leading to dryness of the skin and improvement of existing acne vulgaris has been reported as well as; transient patchy loss and reduced growth of body hair, increased growth of scalp hair, lightening of hair colour and female type of pubic hair growth.

Musculoskeletal and connective tissue disorders
Not known: Osteoporosis (due to long-term androgen deprivation).

Reproductive system disorders
Inhibition of spermatogenesis:
Very common: Sperm count and the volume of ejaculate are reduced.

Infertility is usual, and there may be azoospermia after 8 weeks. There is usually slight atrophy of the seminiferous tubules. Follow-up examinations have shown these changes to be reversible, spermatogenesis usually reverting to its previous state about 3-5 months after stopping Androcur, or in some users, up to 20 months. That spermatogenesis can recover even after very long treatment is not yet known. There is evidence that abnormal sperms which might give rise to malformed embryos are produced during treatment with Androcur.

Gynaecomastia:
Common: Gynaecomastia (sometimes combined with tenderness to touch of the mamillae) which usually regresses after withdrawal of the preparation.
Rare: Galactorrhoea and tender benign nodules have been reported.

Symptoms mostly subside after discontinuation of treatment or reduction of dosage.

General disorders and administration site conditions
Common: Hot flushes, sweating, fatigue and lassitude.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been no reports of ill-effects from overdosage, which it is, therefore, generally unnecessary to treat. There are no specific antidotes and if treatment is required it should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, antiandrogens,

plain, ATC code: G03HA01

Cyproterone acetate acts as an antiandrogen by blocking androgen receptors. It also has progestogenic activity, which exerts a negative feedback effect on hypothalamic receptors, so leading to a reduction in gonadotrophin release, and hence to diminished production of testicular androgens. Sexual drive and potency are reduced and gonadal function is inhibited.

An occasional tendency for the prolactin levels to increase slightly has been observed under higher doses of cyproterone acetate.

Meningioma

Based on results from a French epidemiological cohort study, a cumulative dose-dependent association between cyproterone acetate (CPA) and meningioma has been observed. This study was based on data from the French Health insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg CPA tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose CPA (cumulative dose ≥3 g) and women who were slightly exposed to CPA (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

Incidence and risk of meningioma with different cumulative doses of CPA

Cumulative dose of cyproterone acetate	Incidence rate (in patient-years)	HR_{adj} (95% CI) [a]
Slightly exposed (<3 g)	4.5/100,000	Ref.
Exposed to ≥3 g	23.8/100,000	6.6 [4.0-11.1]
12 to 36 g	26/100,000	6.4 [3.6-11.5]
36 to 60g	54.4/100,000	11.3 [5.8-22.2]
more than 60 g	129.1/100,000	21.7 [10.8-43.5]

[a] Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 36 g for example can correspond with one year of treatment with
100 mg/day.

5.2 Pharmacokinetic properties

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range. The ingestion of two cyproterone acetate 50 mg tablets gives maximum serum levels of about 285 ng/ml at about 3 hours. Thereafter, drug serum levels declined during a time interval of typically 24 to 120 h, with a terminal half-life of 43.9 ± 12.8 h.. The total clearance of cyproterone acetate from serum is 3.5 ± 1.5 ml/min/kg. Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15ß-hydroxy derivative.

Some drug is excreted unchanged with bile fluid. Most of the dose is excreted in the form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion proceeds with a half-life of 1.9 days. Metabolites from plasma are eliminated at a similar rate (half-life of 1.7 days).

Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 - 4 % of total drug levels are present unbound. Because protein binding is non-specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

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

5.3 Preclinical safety data

Systemic toxicity
Preclinical data reveal no specific risk for humans based on conventional studies of repeated dose toxicity beyond those discussed in other sections of the SPC.
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 (300mg/day).

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 the DNA-adduct level in the dog liver cells was extremely low.

This DNA-adduct formation occurred at 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 preneoplastic, 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 mutation. The clinical relevance of these findings is presently uncertain.

In long-term carcinogenicity studies in rats cyproterone acetate increased the incidence of liver tumours including carcinomas at high doses which concomitantly caused liver toxicity and exceeded the maximum human dose. Further investigations into rodents at lower, non-hepatotoxic doses revealed benign liver proliferations similar to effects described for other steroid hormones. However, it must be borne in mind that sex steroids can promote the growth of certain hormone dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Povidone 25 000
Silicon dioxide (aerosil) (E551)
Magnesium stearate (E572)

6.2 Incompatibilities

None known

6.3 Shelf life

5 years

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

PVC/Aluminium blister pack.

Pack size: 60 tablets

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

ADVANZ PHARMA Limited
Unit 17, Northwood House,
Northwood Crescent, Dublin 9,
Ireland D09 V504

8 MARKETING AUTHORISATION NUMBER(S)

PL 56734/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 May 2008

10 DATE OF REVISION OF THE TEXT

15/10/2024