Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Androcur 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg cyproterone acetate.

Excipient with known effect
Each tablet contains 184 mg lactose (as monohydrate), please see section 4.4 for further information.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White to faintly yellowish capsule-shaped tablet imprinted on the upper surface with 'LA' on both sides of a score and with an equilateral hexagon on the lower surface. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Antiandrogen treatment in inoperable carcinoma of the prostate
- Reduction of drive in sexual deviations in men, cyproterone acetate 100 mg can be used when other interventions are considered inappropriate

4.2 Posology and method of administration

Posology
1 tablet twice to three times daily (= 200 – 300 mg). The maximum daily dose is 300mg.

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

The therapy should not be discontinued nor the dose reduced once improvement or remission occurs.

To reduce the initial increase of androgens in combination therapy with GnRH agonists:
Initially 1 tablet Androcur 100 twice daily (= 200 mg) alone for 5 – 7 days, followed by 1 tablet Androcur 100 twice daily (= 200 mg) for 3 – 4 weeks together with a GnRH agonist in the dosage recommended by the marketing authorisation holder (see prescribing information of GnRH agonist).
To treat hot flushes in patients under combination therapy with GnRH analogues or who have had orchiectomy: ½ - 1½ tablets per day (50 – 150 mg) with upward titration up to 1 tablet three times daily (300 mg) if necessary.

Reduction of drive in sexual deviation:
Generally, treatment is started with 50 mg twice daily. It may be necessary to increase the dose to 100 mg twice daily, or even 100 mg three times daily for a short period of time. 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. Quite often 25 mg twice daily is sufficient. When establishing the maintenance dose, when changing the dose or when discontinuing cyproterone acetate, one should not adjust the dosage abruptly, this should be done gradually. To this end, the daily dose should be reduced by 50 mg or, better, 25 mg at intervals of several weeks.
To stabilise the therapeutic effect, it is necessary to take Androcur 100 over a protracted period of time, if possible with the simultaneous use of psychotherapeutic measures.

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.

Elderly population
There are no data suggesting the need for a dosage adjustment in elderly patients.

Hepatic impairment
The use of Androcur is contraindicated in patients with liver diseases (i.e. as long as liver function values have not returned to normal).

Renal impairment
There are no data suggesting the need for a dosage adjustment in patients with renal impairment.

Method of administration
Oral use

4.3 Contraindications

Use for reduction of drive in sexual deviations

- Liver diseases
- Dubin-Johnson syndrome, Rotor syndrome
- Previous or existing liver tumours
- Presence or history of meningioma
- Wasting diseases
- Severe chronic depression
- Previous or existing thromboembolic processes
- Severe diabetes with vascular changes
- Sickle-cell anaemia
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Use as antiandrogen treatment in inoperable carcinoma of the prostate

- 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)
- Presence or history of meningioma
- Wasting diseases (with the exception of inoperable carcinoma of the prostate)
- Severe chronic depression
- Existing thromboembolic processes
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Initiation of anti-androgen therapy and its overall direction should only be carried out by specialists.

Meningioma

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 100 mg tablets is diagnosed with meningioma, treatment with Androcur 100 mg tablets and other cyproterone-containing products must be permanently stopped (see section 4.3 Contra-indications).
There is some evidence that the meningioma risk may decrease after treatment discontinuation of cyproterone.

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 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, at regular intervals during treatment and whenever 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 intraabdominal hemorrhage 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 included in the differential-diagnostic considerations.

Thromboembolic events

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 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.

Anemia

Anemia has been reported during treatment with Androcur. Therefore, the red-blood cell count should be checked regularly during treatment.

Diabetes mellitus

Strict medical supervision is necessary if the patient suffers from diabetes, because the requirement for oral anti-diabetics or insulin can change during Androcur treatment (see also section 'Contraindications').

Shortness of breath

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.

Adrenocortical function

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

Other conditions

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Although clinical interaction studies have not been performed, since this drug is metabolized 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 e.g. 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 therapeutic cyproterone acetate 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 metabolized by CYP3A4, are coadministered with high therapeutic cyproterone acetate doses since they share the same metabolic pathway.

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

4.6 Fertility, pregnancy and lactation

Treatment with Androcur 100 (for use in men) is not indicated in women.

4.7 Effects on ability to drive and use machines

Androcur 100 mg can lead to tiredness and diminished vitality and can impair the ability to concentrate. Patients receiving the drug should not drive or operate machinery unless it has been shown not to effect physical or mental ability.

4.8 Undesirable effects

Summary of the safety profile

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 adverse drug reactions (ADRs) in patients receiving Androcur are hepatic toxicity, benign and malignant liver tumors which may lead to intra-abdominal hemorrhage, and thromboembolic events.

Tabulated list of adverse reactions

The frequencies of ADRs reported with Androcur are summarized in the table below. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1,000 and < 1/100), rare (≥ 1/10,000 and < 1/1,000) and very rare (< 1/10,000). The ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated are listed under "not known".

System organ class MedDRA v. 8.0	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Neoplasms benign, malignant and unspecified				Mening-ioma §)*)	Benign and malignant liver tumors*)	
Blood and lymphatic system disorders						Anemia*)
Immune system disorders				Hyper-sensitivity reaction		
Metabolism and nutrition disorders		Weight increased or weight decreased				

Psychiatric disorders	Libido decreased, erectile dysfunction	Depressed mood, Restlessness (temporary)				
Vascular disorders						Thrombo-embolic event*)**)
Respiratory, thoracic and mediastinal disorders		Shortness of breath*)				
Gastro-intestinal disorders						Intra-abdominal hemorrrhage*)
Hepato-biliary disorders		Hepatic toxicity, including jaundice, hepatitis, hepatic failure*)				
Skin and subcutaneous tissue disorders			Rash			
Musculoskeletal and connective tissue disorders						Osteo-porosis
Reproductive system and breast disorders	Reversible inhibition of spermatogenesis	Gynaeco-mastia				
General disorders and administration site conditions		Fatigue, Hot flushes, Sweating				

§) See section 4.3 Contra-indications
*) For further information see section 'Special warnings and precautions for use'.
**) A causal relationship with Androcur has not been established.

Description of selected adverse reactions

The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate (see section 4.4).

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.

Androcur may lead to gynaecomastia (sometimes combined with tenderness to touch of the mammillae) which usually regresses after withdrawal of the preparation.

As with other antiandrogenic treatments, long-term androgen deprivation with Androcur may lead to osteoporosis.

The most appropriate MedDRA term (version 8.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

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: HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Acute toxicity studies following single administration showed that cyproterone acetate, the active ingredient of Androcur, can be classified as practically non-toxic. Nor is any risk of acute intoxication to be expected after a single inadvertent intake of a multiple of the dose required for therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiandrogens, plain

ATC code: G03HA01

Androcur is an antiandrogenic hormone preparation.

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

Cyproterone acetate inhibits competitively the effect of androgens at androgen-dependent target organs, e.g. it shields the prostate from the effect of androgens originating from the gonads and/or the adrenal cortex.

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.

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.

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 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 cyproterone tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥3 g) and women who were slightly exposed to cyproterone acetate (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

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 12g for example can correspond with one year of treatment with 50 mg/day for 20 days each month.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range.
The absolute bioavailability of cyproterone acetate is almost complete (88 % of dose).

Distribution

The ingestion of 100 mg of cyproterone acetate gives maximum serum levels of about 239.2 ± 114.2 ng/ml at 2.8 ± 1.1 hours. Thereafter, drug serum levels declined during a time interval of typically 24 to 120 h, with a terminal half-life of 42.8 ± 9.7 h. The total clearance of cyproterone acetate from serum was determined to be 3.8 ± 2.2 ml/min/kg.

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.
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.

Metabolism / Biotransformation

Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15ß-hydroxy derivative. Phase 1 metabolism of cyproterone acetate is mainly catalyzed by the cytochrome P450 enzyme CYP3A4.

Elimination

Some dose parts are 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 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).

5.3 Preclinical safety data

Systemic toxicity
Preclinical data reveal no specific risk for humans based on conventional studies of repeated dose toxicity.

Reproduction toxicity
The temporary inhibition of fertility in male rats brought about by daily oral treatment did not in any way indicate that Androcur treatment leads to spermatozoa damage which could lead to malformations or impairment of fertility in the offspring.

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 dog liver cells was extremely low.

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 the mutation frequency in transgenic rats carrying a bacterial gene as a 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.

On the whole, the available data do not raise any objection to the use of Androcur in humans if used in accordance with the directions for the given indications and at the recommended dosages.

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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate (E 572)
Maize starch
Povidone 25,000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each carton contains 6 blister strips of 10 tablets sealed in deep-drawn strips made of polyvinyl chloride film with counter-sealing foil made of aluminium with heat sealable coating.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
1st Floor
The Grange Offices
The Grange
Brewery Road
Stillorgan
Co. Dublin
A94 H2K7
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1410/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 January 1997

Date of last renewal: 24 January 2007

10 DATE OF REVISION OF THE TEXT

November 2022