AUSTRALIAN PRODUCT INFORMATION

CYPRONE 100

Cyproterone acetate tablets

1 NAME OF THE MEDICINE

Cyproterone acetate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Cyprone 100 tablet contains 100 mg of cyproterone acetate as the active ingredient.

Excipients with known effect: Contains sugars (as lactose).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Cyprone 100	:	capsule shaped, biconvex white tablets with 'CPA 100' marked on one side and scored on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Inoperable prostatic carcinoma

- To suppress 'flare' with initial luteinising hormone releasing hormone (LHRH) analogue therapy;
- long-term palliative treatment where LHRH analogues or surgery are ineffective, not tolerated, contraindicated or where oral therapy is preferred;
- treatment of hot flushes in patients treated with LHRH analogues or who have had orchidectomy.

4.2 DOSE AND METHOD OF ADMINISTRATION

The maximum daily dose is 300 mg.

Inoperable prostatic carcinoma

Cyprone 100 should be taken with some liquid after a meal.

To reduce the initial increase of male sex hormones ('flare') in treatment with luteinising hormone releasing hormone (LHRH) agonists

Initially 1 Cyprone 100 tablet twice daily (i.e. 200 mg a day) alone for five to seven days, followed by 1 tablet Cyprone 100 twice daily (i.e. 200 mg a day) for three to four weeks together with an LHRH agonist in the dosage recommended by the manufacturer.

In long-term palliative treatment of advanced prostate cancer in patients who have not had an orchiectomy

100 mg (1 tablet Cyprone 100) two to three times daily. Treatment should not be interrupted nor the dosage reduced after improvement or remissions have occurred.

To treat hot flushes in patients under treatment with luteinising hormone releasing hormone analogues or who have had orchiectomy

50 mg to 150 mg (half to one and a half tablets) per day with upward titration up to 1 tablet three times daily (300 mg) if necessary.

Paediatric use

Cyprone 100 tablets are not recommended for use in male children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Use in the elderly

There is no data suggesting the need for dosage adjustment in elderly patients.

Patients with hepatic impairment

The use of Cyprone 100 tablets is contraindicated in patients with liver diseases.

Patients with renal impairment

There is no data suggesting the need for dosage adjustment in patients with renal impairment.

4.3 CONTRAINDICATIONS

- 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 any of the components of Cyprone 100

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cyprone 100 is for use only in men

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

As with other anti-androgenic treatments, in male patients long-term androgen deprivation with Cyprone 100 may lead to osteoporosis.

In men of procreative age, for whom fertility could be important after conclusion of the medication, it is advisable to make at least one control spermatogram as a precaution before the start of treatment in order to counter any unjustified claims of later infertility as a result of the antiandrogen therapy. Spermatogenesis has taken 3 to 20 months to return to normal after discontinuing therapy.

Use in hepatic impairment

Liver

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, has been observed in patients treated with cyproterone acetate. At dosages of 100 mg and above, cases with fatal outcome have been reported. Most reported fatal cases were in men with advanced carcinoma of the prostate. Toxicity is dose related and usually develops several months after treatment has begun. Liver function tests should be performed pre-treatment, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, Cyprone 100 should be withdrawn unless hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case Cyprone 100 should be continued only if the perceived benefit outweighs the risk.

Cases of benign and malignant liver tumours, which may lead to life-threatening intra-abdominal haemorrhage, have been observed after the use of Cyprone 100. 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.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with long-term use (years) of Cyproterone acetate at doses of 25 mg/day and above. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate. If a patient treated with Cyprone 100 is diagnosed with meningioma, treatment with cyproterone containing products, including Cyprone 100 must be permanently stopped (see Section 4.3 CONTRAINDICATIONS).

Diabetes

Strict medical supervision is necessary if the patient suffers from diabetes, because the requirement for oral antidiabetics or insulin can change during Cyprone 100 treatment (see Section 4.3 CONTRAINDICATIONS).

Shortness of breath

A sensation of shortness of breath may occur under high-dosed treatment with Cyprone 100. 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 alkalosis and which is not considered to require treatment.

Thromboembolic events

The occurrence of thromboembolic events has been reported in patients using Cyprone 100 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 Cyprone 100 is prescribed.

Adrenocortical function

During treatment adrenocortical function should be checked regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of Cyprone 100 with high doses.

Anaemia

Anaemia has been reported during treatment with Cyprone 100. Therefore, the red-blood cell count should be checked regularly during treatment.

Other conditions

Cyprone 100 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose mal-absorption should not take this medicine.

The sexual drive-reducing effect of Cyprone can be diminished under the influence of alcohol.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric Use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The requirement for oral antidiabetics or insulin can change.

Although clinical interaction studies have not been performed, since this drug 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, e.g. rifampicin, phenytoin and products containing St. John's wort (*Hypericum perforatum*) may reduce the levels of cyproterone acetate.

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 cyproterone acetate doses since they share the same metabolic pathway.

Based on *in vitro* CYP450 studies, the recommended clinical doses are likely to inhibit CYP2C8, and an inhibition of the CYP 2C9, 2C19, 3A4 and 2D6 is also possible at high therapeutic cyproterone acetate doses of 100 mg three times daily.

4.6 FERTILITY, PREGNANCY AND LACTATION

CYPRONE 100 IS FOR USE ONLY IN MEN

Effects on Fertility

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.1 PHARMACODYNAMIC PROPERTIES.

Use in Pregnancy

No data available.

Use in Lactation

No data available.

4.7 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 Cyprone 100 can lead to tiredness and diminished vitality and can impair the ability to concentrate.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions reported in clinical trials.

The following adverse reactions have been reported at the approximate frequencies (not necessarily implicating a causal relationship) indicated below:

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
Very rare	<1/10,000

General

Very common: tiredness, weight increase

Common: headache, depressive moods

Cardiovascular

Common: thrombotic phenomena

Gastrointestinal

Common: nausea and other gastrointestinal complaints

Reproductive

Very common: diminished libido

Common: mastodynia

Skin

Rare: rash

The most frequently observed adverse drug reactions (ADRs) in patients receiving Cyprone 100 are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious ADRs in patients receiving Cyprone 100 are hepatic toxicity, benign and malignant liver tumours which may lead to intra-abdominal haemorrhage and thromboembolic events.

Over the course of several weeks Cyprone 100 gradually impairs spermatogenesis as a result of the antiandrogenic and antigonadotropic actions. Spermatogenesis recovers gradually within several months of discontinuing therapy.

Cyprone 100 may lead to gynaecomastia (sometimes combined with tenderness to touch of the breast) which usually regresses after withdrawal of the preparation or reduction of the dose.

As with other antiandrogenic treatments, in male patients, long-term androgen deprivation with Cyprone 100 may lead to osteoporosis.

In individual cases, disturbances of liver function, some of them severe, have been reported with high dosed Cyprone 100 treatment.

Changes in bodyweight are possible.

Other adverse events reported at a low incidence are skin discolouration and striae.

Post-marketing information

The following adverse effects have been reported in users of cyproterone acetate and are based on post-marketing data and cumulative experience with Cyprone.

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

System organ class (MedDRA)	**Very common** ≥ **1/10**	**Common** ≥ **1/100 and < 1/10**	**Uncommon** **> 1/1000 and < 1/100**	**Rare** **> 1/10000 and <1/1000**	**Very rare** **< 1/10000**
Neoplasms benign and malignant					Benign and malignant liver tumours*

Blood and lymphatic system disorder					
Immune system disorder				Hypersensitivity reaction	
Metabolism and nutrition disorder		Weight increased or weight decreased			
Psychiatric disorder	Libido decreased, erectile dysfunction	Depressed mood, restlessness (temporary)			
Skin and subcutaneous tissue disorder			Rash		
Musculoskeletal and connective tissue disorder					Osteoporosis
Hepatobiliary disorder		Hepatic toxicity including jaundice, hepatitis, hepatic failure*		Increased liver enzymes	Liver function disturbance
Gastrointestinal disorder					Nausea, GI complaints
Respiratory, thoracic and Mediastinal disorder		Shortness of breath*			
Cardiovascular disorder					Thrombotic phenomena, tachycardia
Reproductive system and breast disorder	Reversible inhibition of spermatogenesis	Gynaecomastia			Breast tenderness, breast pain
General disorders and administration site condition		Fatigue, hot flushes, sweating			Tiredness, sleep disturbances

*For further information see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.
†A causal relationship with Cyprone 100 has not been established

The ADRs identified only during post-marketing surveillance and for which a frequency could not be estimated are: anaemia*, meningioma, intra-abdominal haemorrhage*, thromboembolic events *†

Under treatment with Cyprone 100, sexual drive and potency are reduced and gonadal function is inhibited. These changes are reversible after discontinuation of therapy.

Meningiomas have been reported in association with long-term use (several years) of cyproterone doses of 25 mg and above (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no clinical experience in overdose. Assessment and symptomatic treatment should be initiated as required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Cyprone 100 is an anti-androgenic hormone preparation.

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. Prostatic carcinoma and its metastases are in general androgen dependent, cyproterone acetate therefore exerts a direct anti-androgenic action on the tumour and its metastases.

Cyproterone acetate in addition has a progestogenic action exerting a negative feedback effect centrally on the hypothalamic receptors, so leading to a reduction in gonadotropin release, and hence to diminished production of testicular androgens. Treatment with cyproterone acetate in men results in a reduction of sexual drive and potency and inhibition of gonadal function. These changes are reversible following discontinuation of the therapy.

The antigonadotropic effect of cyproterone acetate is also exerted when the substance is combined with luteinising hormone releasing hormone (LHRH) agonists. The initial increase of testosterone provoked by this substance group is decreased by cyproterone acetate.

Prolactin levels can increase slightly under higher doses of cyproterone acetate. Studies showed increased prolactin levels up to 20 ng/mL (normal range 5 to 15 ng/mL). There are no data for periods longer than six months.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

The ingestion of 100 mg cyproterone acetate gives maximum serum levels of 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 hours, with a terminal half-life of 42.8 ± 9.7 hours. The total clearance of cyproterone acetate from serum was determined to be 3.8 ± 2.2 mL/minute/kg. The absolute bioavailability of cyproterone acetate is unknown. Relative bioavailability was calculated, in a study of eight young women, from a dose corrected comparison of area under the curves of serum levels after 100mg oral and 300 mg intramuscular depot administration and was found to be 80 ± 30% when averaged over all volunteers (range 23 to 119%).

Distribution

The major part of circulating cyproterone acetate is bound to serum albumin. In a study in 15 women receiving 2 mg cyproterone acetate in combination with 35 µg ethinylestradiol, the free fraction of cyproterone acetate was about 3.5 to 4%. Because protein binding is non-specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

Metabolism

Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15ß-hydroxy derivative. Some dose parts are excreted unchanged with bile fluid. Phase I metabolism of cyproterone acetate is mainly catalysed by the CYP450 enzyme CYP3A4.

Excretion

In a study in six women administered a ^{14}C labelled dose of 2 mg cyproterone acetate (CPA) in combination with 50 µg oestrogen, approximately 30% of the label was found in the urine and 58% in the faeces. 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).

Steady-state conditions

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 three can be expected in the serum during repeated daily administration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cyproterone acetate was negative in a standard battery of genotoxicity studies. However, further tests showed that cyproterone acetate was capable of producing hepatocyte DNA adducts in rats, dogs and monkeys (and an increase in DNA repair activity in rats) *in vivo* and also in freshly isolated rat and human liver cells *in vitro*. This DNA adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for Cyprone 100. *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 mutation. The clinical relevance of these findings presently remains uncertain

Carcinogenicity

Long-term animal carcinogenicity studies were performed in rats and mice. In one rat study, an increased incidence of hepatomas was reported at oral dose levels of 50 mg/kg cyproterone acetate and above. In mouse (and a second rat) carcinogenicity studies, increases in benign proliferative changes (nodular hyperplasia) in liver cells of female mice and male and female rats were reported at oral doses of 2 mg/kg. Because of shortcomings in these studies (inadequate pharmacokinetic data and the need to reassess the liver pathology), the carcinogenic potential of cyproterone acetate in animals could not be determined.

Clinical experience and limited epidemiological data available to date do not appear to have supported an increased incidence of hepatic tumours in humans. However, it must be borne in mind that steroidal sex hormones can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients: lactose monohydrate, maize starch, povidone, pregelatinised maize starch, magnesium stearate, colloidal anhydrous silica.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al foil blisters

Pack size: 50 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

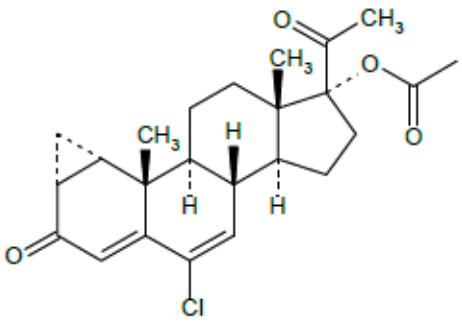
6.7 PHYSICOCHEMICAL PROPERTIES

Cyproterone acetate is a white to pale yellow crystalline powder. Cyproterone acetate is very soluble in chloroform and dioxane, freely soluble in acetone and benzene, soluble in ethanol, methanol and ethyl acetate, sparingly soluble in solvent hexane, and almost insoluble in water.

Chemical Structure

Chemical name : 6-chloro-17α hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione acetate

Structural formula :



Molecular formula : $C_{24}H_{29}ClO_4$ Molecular weight : 416.9

CAS Number

427-51-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

1 June 2016

10 DATE OF REVISION

04/02/2021

Summary Table of Changes

Section Changed	Summary of New Information
4.4; 5.2; 6.4	Minor editorial changes
4.2	Update subheading from ‘Children’ to ‘Paediatric’
4.4	Additional information on meningioma
6.7	Corrected chemical name; added new chemical structure image

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