PRODUCT INFORMATION

Cyprone 100

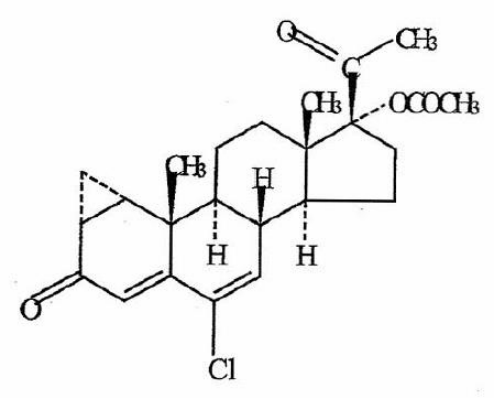
Cyproterone acetate

NAME OF THE MEDICINE

Active ingredient : cyproterone acetate

Chemical name : 6-chloro-3,20-dioxo-1beta,2beta-dihydro-3 H-cyclopropa [1,2] pregna-1.,4,6-trien, 17-yl acetate

Structural formula :



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

Molecular weight : 416.9

CAS Registry no. : 427-51-0

DESCRIPTION

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 hexane, and almost insoluble in water.

Each Cyprone 100 tablet contains cyproterone acetate 100 mg. Excipients: lactose, maize starch, Povidone, pregelatinised maize starch, magnesium stearate, colloidal anhydrous silica.

PHARMACOLOGY

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 nanogram/mL (normal range 5 to 15 nanogram/mL). There are no data for periods longer than six months.

Pharmacokinetics

Absorption

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

The ingestion of cyproterone acetate 100 mg gives maximum serum levels of 239.2 +/- 114.2 nanogram/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 cyproterone acetate 2 mg in combination with ethinyloestradiol 35 microgram, the free fraction of cyproterone acetate was about 3.5 to 4%. Because protein binding is nonspecific, 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 15beta- hydroxy derivative. Some dose parts are excreted unchanged with bile fluid. Phase I metabolism of CPA is mainly catalysed by the CYP450 enzyme CYP3A4.

Excretion

In a study in six women administered a 14C labelled dose of cyproterone acetate (CPA) 2 mg in combination with oestrogen 50 microgram, 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.

In a study comparing Cyproterone 50 mg tablets with the reference (Androcur 50 mg) tablets, the two products were shown to be bioequivalent. The geometric mean ratio and 90% confidence intervals for cyproterone $AUC_{0-\infty}$ were found to be 1.019, and 0.963 to 1.079, respectively, while those for C_{max} were 0.958, and 0.880 to 1.044, respectively.

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.

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).
- 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

PRECAUTIONS

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 spem1atogram 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.

Direct hepatic toxicity, including jaundice, hepatitis and liver failure, which has been fatal in some cases, has been reported in patients treated with cyproterone acetate. At dosages of 100 mg and above, cases with fatal outcome have been reported. Most reported cases are in men with carcinoma of the prostate. Toxicity is dose related and usually develops several months after treatment has begun. Liver function tests should be performed pretreatment, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, Cyprone 100 should normally 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 tumors, which may lead to life-threatening intra- abdominal hemorrhage, 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.

The occurrence of meningiomas (single and multiple) has been reported in association with longterm use (years) of Cyproterone acetate at doses of 25 mg /day and above. If a patient treated with Cyprone 100 is diagnosed with meningioma, treatment with Cyprone 100 must be stopped. (see **CONTRAINDICATIONS**)

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 **CONTRAINDICATIONS**).

A sensation of shortness of breath may occur in individual cases 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.

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.

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

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

Genotoxicity

Cyproterone acetate was negative in a standard battery of genotoxicity studies. However, further tests showed that CPA 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 CPA 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 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 CPA 50 mg/kg 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 CPA 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.

Effect on ability to drive or operate machinery

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.

INTERACTIONS WITH OTHER MEDICINES

The requirement for oral anti-diabetics 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 coadministered 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.

ADVERSE 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 greater than or equal to 1/10; common greater than or equal to 1/100 and <1/10; uncommon greater than or equal to 1/1,000 and< 1/100; rare greater than or equal to 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 patient’s 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.

Postmarketing information

The following adverse effects have been reported in users of cyproterone acetate (postmarketing data) but for which the association to Cyprone 100 has neither been confirmed nor refuted.

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 tumor
Blood and lymphatic system disorder				Hypersensitivity reaction	
Immune system disorder					
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	Increased liver
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 **PRECAUTIONS**

†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 *†

Meningiomas have been reported in association with long-term use (several years) of cyproterone of 25 mg and above (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

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

DOSAGE AND 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. 200mg a day) alone for five to seven days, followed by 1 Cyprone 100 tablet 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 Cyprone 100 tablet) 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 to 150 mg (1/2 to 1 1/2 tablets) per day with upward titration up to 1 tablet three times daily (300 mg) if necessary.

Children and adolescents

Cyprone 100 tablets 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.

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

OVERDOSAGE

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

In cases of overdose, it is advisable to contact the Poisons Information Centre (131 126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Cyprone 100	:	capsule shaped, biconvex white tablets with 'CPA 100' marked on one side and scored on the other. Cyprone 100 tablets presented in PVC/PVDC/Al foil blisters. Each pack contains 50 tablets. Store below 25 degrees Celsius. Protect from light

NAME AND ADDRESS OF THE SPONSOR

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Millers Point NSW 2000

ABN 93 002 359 739

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

1 June 2016

DATE OF MOST RECENT AMENDMENT

28 February 2017