CYPROSTAT® 100mg PRODUCT INFORMATION

NAME OF THE MEDICINE

Cyprostat 100mg

Each pack contains tablets with 100mg cyproterone acetate.

Cyproterone acetate:

\[
\text{Chemical Name: 6-chloro-17\alpha \text{ hydroxy-1\alpha,2\alpha-methylene-pregna-4,6-diene-3,20-dione acetate}}
\]

\[
\text{Molecular Formula: C_{24}H_{29}ClO_4}
\]

\[
\text{Molecular Mass: 416.96}
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\[
\text{CAS No.: 427-51-0}
\]

DESCRIPTION

Cyproterone acetate is a white to pale yellow crystalline powder. M.P. 206-213°C. 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.

PHARMACOLOGY

Cyprostat is an antiandrogenic 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 antiandrogenic 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 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 20ng/mL (normal range 5-15ng/mL). There are no data for periods longer than 6 months.

**Pharmacokinetic properties**

**Absorption**

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

The ingestion of 100mg of cyproterone acetate gives maximum serum levels of 239.2±114.2ng/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±9.7h. The total clearance of cyproterone acetate from serum was determined to be 3.8±2.2mL/min/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 300mg intramuscular depot administration and was found to be 80±30% when averaged over all volunteers (range 23%-119%).

**Distribution**

The major part of circulating cyproterone acetate is bound to serum albumin. In a study in 15 women receiving 2mg cyproterone acetate in combination with 35μg ethinyloestradiol, the free fraction of cyproterone acetate was about 3.5-4%. 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 15β-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.

**Elimination**

In a study in 6 women administered a 14C labelled dose of 2mg cyproterone acetate in combination with 50μg 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 3 can be expected in the serum during repeated daily administration.
INDICATIONS

Inoperable prostatic carcinoma
- to suppress "flare" with initial LHRH analogue therapy
- in long term palliative treatment where LHRH analogues or surgery are ineffective, not tolerated, contraindicated or where oral therapy is preferred
- in the 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)
- 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 Cyprostat 100mg

PRECAUTIONS

CYPROSTAT-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 antiandrogenic treatments, in male patients long-term androgen deprivation with Cyprostat 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 3-20 months to return to normal after discontinuing therapy.

Liver

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure has been observed in patients treated with cyproterone acetate. At dosages of 100mg 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 develops, usually, 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, Cyprostat should be withdrawn, unless hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case Cyprostat 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 cyproterone acetate. 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 25mg/day and above. If a patient treated with Cyprostat is diagnosed with meningioma, treatment with Cyprostat must be stopped (see CONTRAINDICATIONS).

Diabetes

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

Shortness of breath

A sensation of shortness of breath may occur under high-dosed treatment with Cyprostat. 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 Cyprostat 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 Cyprostat 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 Cyprostat with high doses.

Anaemia

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

Other conditions

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

Carcinogenicity and mutagenicity

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 Cyprostat. 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.

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 50mg/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 2mg/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.

**Interactions with other medicines**

The requirement for oral antidiabetics or insulin can change.

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.

The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMGCoA inhibitors (statins), which are primarily metabolized by CYP 3A4, 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 3 times 100 mg per day.

**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 Cyprostat can lead to tiredness and diminished vitality and can impair the ability to concentrate.

**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:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Approximate Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥ 1/100 and &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥ 1/1,000 and &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥ 1/10,000 and &lt;1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000</td>
</tr>
</tbody>
</table>
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 Cyprostat are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

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

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

Cyprostat 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 Cyprostat may lead to osteoporosis.

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

Changes in body weight 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 (post-marketing data) but for which the association to Cyprostat 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.
<table>
<thead>
<tr>
<th>System organ class (MedDRA)</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms benign and malignant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benign and malignant liver tumours*</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Immune system disorders</td>
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<td></td>
<td></td>
<td></td>
<td>Hypersensitivity reaction</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight increased or Weight decreased</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Libido decreased, Erectile dysfunction</td>
<td>Depressed mood Restlessness (temporary)</td>
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<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td>Rash</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
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<td></td>
<td>Osteoporosis</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic toxicity, including jaundice, hepatitis, hepatic failure*</td>
<td>Increased liver enzymes</td>
<td></td>
<td>Liver function disturbance</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
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<td></td>
<td>Nausea GI complaints</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td>Shortness of breath*</td>
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<tr>
<td>Cardiovascular disorders</td>
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<td></td>
<td></td>
<td>Thrombotic phenomena Tachycardia</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Reversible inhibition of spermatogenesis</td>
<td></td>
<td></td>
<td></td>
<td>Breast tenderness Breast pain</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue Hot flushes Sweating</td>
<td></td>
<td></td>
<td>Tiredness Sleep disturbances</td>
<td></td>
</tr>
</tbody>
</table>

* For further information see PRECAUTIONS
† A causal relationship with Cyprostat 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 Cyprostat, 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 Cyprostat doses of 25mg and above (see CONTRAINDICATIONS and PRECAUTIONS).

**DOSAGE AND ADMINISTRATION**

The maximum daily dose is 300mg.

**Inoperable prostatic carcinoma**

Cyprostat tablets should be taken with some liquid after a meal.
To reduce the initial increase of male sex hormones (‘flare’) in treatment with LHRH agonists

Initially 1 tablet Cyprostat twice daily (i.e. 200mg a day) alone for 5-7 days, followed by 1 tablet Cyprostat twice daily (i.e. 200mg a day) for 3-4 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

100mg (1 tablet Cyprostat) 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 LH-RH analogues or who have had orchiectomy

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

Children and adolescents

Cyprostat 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 are no data suggesting the need for dosage adjustment in elderly patients.

Patients with hepatic impairment

The use of Cyprostat is contraindicated in patients with liver diseases.

Patients with renal impairment

There are 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 (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Cyprostat 100mg - blisters of 50 capsule shaped white scored tablets.

PBS availability (Authority required): Tablets 100mg – Max Qty 50; Rpts 5.

Store below 30°C.

Each Cyprostat tablet contains 100mg cyproterone acetate
Excipients
lactose
maize starch
povidone
magnesium stearate

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Limited
ABN 22 000 138 714
875 Pacific Highway
Pymble, NSW 2073

POISON SCHEDULE OF MEDICINE

S4

DATE OF TGA APPROVAL

30 August 2007

Date of most recent amendment: 9 November 2010

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