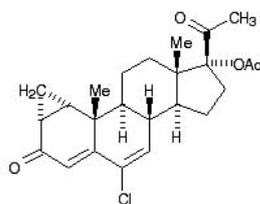


PRODUCT INFORMATION CYPROTERONE SANDOZ® 100mg TABLETS

NAME OF THE MEDICINE

Cyproterone acetate

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



CAS [427-51-0]

Empirical formula: C₂₄H₂₉ClO₄.

MW:416.94.

DESCRIPTION

Active: cyproterone acetate.

Excipients: lactose, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate.

Cyproterone Sandoz 100 mg AUST R 107331

Cyproterone acetate is a white to pale yellow crystalline powder. Melting point: 206 to 213°C. It 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

Pharmacodynamics

Cyproterone acetate is believed to prevent the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. The stimulating effect of male sex hormones on androgen dependent structures and functions is weakened or counteracted by cyproterone acetate.

Cyproterone acetate also exerts a progestational and anti-gonadotrophic effect.

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 function of androgen dependent target organs, such as the prostate, is restricted.

Prostatic carcinoma and its metastases are in general androgen dependent. Cyproterone acetate exerts a direct antiandrogenic action on the tumour and its metastases, and in addition it exerts a negative feedback effect on the hypothalamic receptors, so leading to a reduction in gonadotropin release, and hence to diminished production of testicular androgens.

Serum prolactin levels may increase with higher doses of CPA. Prolactin levels increased up to 20ng/mL (normal range 5-15ng/mL) in studies of up to six months duration.

Pharmacokinetics

Absorption. Following oral administration, cyproterone acetate is absorbed slowly. Relative bioavailability was calculated from a dose-corrected comparison of area under the curves of serum levels after 100mg oral and 300mg intramuscular depot administration in 8 young women, and was found to be $80 \pm 30\%$ (range 23% - 199%). In a study to determine the bioequivalence of Cyproterone Sandoz 100mg in comparison to cyproterone acetate 100mg tablets distributed by Schering Proprietary Ltd, the mean peak plasma concentration for cyproterone acetate from the Cyproterone Sandoz 100mg formulation after administration of a single 100mg dose, was 176.2ng/mL at about 4 hours in comparison to 161.7ng/mL after about 3 hours for the reference product. The 90% Confidence Interval (CI) for comparison of the log transformed peak concentrations was 0.97 – 1.22. The Area Under the Plasma Concentration-Time curve ($AUC_{0-\infty}$) was 5756.0ng.h/mL for Cyproterone Sandoz 100mg versus 5953.3ng.h/mL for 100mg cyproterone acetate tablets distributed by Schering Proprietary Ltd with the 90% Confidence Interval (CI) for comparison of the log transformed data being 0.91 – 1.03.

Distribution. Cyproterone acetate within the cardiovascular system 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. In animals, cyproterone acetate has been shown to distribute into the liver, kidney, brain and heart. Levels in these organs may be higher than in plasma.

Metabolism. Cyproterone acetate is metabolised by various pathways, including hydroxylations and glucuronide conjugations. The main metabolite in human plasma is 15 β -hydroxycyproterone acetate.

Elimination. 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. Unconjugated metabolites appear in the urine whereas glucuronide metabolites appear in the bile. In the study discussed above, cyproterone acetate was eliminated with a mean half-life of approximately 70 hours for both preparations.

Steady state conditions: An accumulation of cyproterone acetate in the serum by a factor of about 3 can be expected during repeated daily administration.

Radioimmunoassays show that about 0.2% of the dose is eliminated with the breast milk.

INDICATIONS

Inoperable prostatic carcinoma. To suppress flare with initial luteinising hormone releasing hormone (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

Hepatic diseases, a history of or existing hepatic tumours (only if these are not due to metastases), Dubin-Johnson syndrome, Rotor syndrome, wasting diseases (with the exception of carcinoma of the prostate), severe chronic depression, previous or existing thromboembolic processes, severe diabetes with vascular changes, sickle-cell anaemia, presence or history of meningioma.

In patients with a history of thromboembolic processes or suffering from sickle-cell anaemia, or from severe diabetes with vascular changes, the risk/benefit ratio must be considered carefully in each individual case before Cyproterone Sandoz 100mg is prescribed.

Hypersensitivity to any of the components of Cyproterone Sandoz 100 mg.

PRECAUTIONS

Cyproterone Sandoz 100mg is for use only in men.

During treatment, hepatic function, adrenocortical function and red blood cell count should be checked regularly. In patients with diabetes, strict medical supervision is necessary. Carbohydrate metabolism should be monitored carefully.

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.

The occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone acetate. However, 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.

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with cyproterone acetate 200 to 300mg daily. Most reported cases are in men with prostatic cancer. Toxicity is dose related and usually develops several months after treatment has begun. Liver function tests should be performed pretreatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless hepatotoxicity can be explained by another cause, eg. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk. Benign and malignant hepatic tumours, leading very rarely to life-threatening intra-abdominal haemorrhage, have been observed in isolated cases after the use of hormonal steroids. If severe upper abdominal complaints, hepatic enlargement or signs of intra-abdominal haemorrhage occur, a hepatic tumour should be included in the differential diagnostic considerations and, if necessary, discontinuation of the preparation considered.

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 Cyproterone Sandoz is diagnosed with meningioma, treatment with Cyproterone Sandoz must be stopped (see **CONTRAINDICATIONS**).

A sensation of shortness of breath may occur in individual cases under high dose treatment with Cyproterone Sandoz 100mg. 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.

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

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

Other conditions

Cyproterone Sandoz 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.

There is a risk of osteoporosis in long-term anti-androgen treatment.

Effects on fertility

Spermatogenesis is impaired during treatment and recovers gradually after discontinuation. See ADVERSE EFFECTS.

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.

The long-term effects on female fertility are not known with certainty.

Use in pregnancy (Category D)

Cyproterone Sandoz 100mg is for use only in men.

Australian Pregnancy Categorisation – Category D. Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Use in elderly

There is reduced hepatic clearance in the elderly, and this should be considered when prescribing and monitoring treatment with Cyproterone Sandoz 100mg.

Carcinogenicity and Genotoxicity

Cyproterone acetate (CPA) 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 Cyproterone Sandoz 100mg. In vivo consequences of CPA 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 CPA 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 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 (eg. road users, machine operators) that Cyproterone Sandoz 100mg can lead to tiredness and diminished vitality and can impair the ability to concentrate.

INTERACTIONS WITH OTHER MEDICINES

The requirement for oral antidiabetics or insulin may 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, e.g. rifampicin, phenytoin and products containing St John's Wort (*Hypericum perforatum*) may reduce 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 CYP3A4, are coadministered with high therapeutic cyproterone acetate doses since they share the same metabolic pathway.

ADVERSE EFFECTS

Adverse effects reported in clinical trials

The following adverse effects 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 commonly reported adverse drug reactions (ADRs) in female patients receiving Cyproterone Sandoz are spotting, weight increase and depressed mood.

The most frequently observed ADRs in male patients receiving Cyproterone Sandoz are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious ADRs in patients receiving Cyproterone Sandoz are hepatic toxicity, benign and malignant liver tumour.

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

In male patients Cyproterone Sandoz occasionally leads 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 Cyproterone Sandoz may lead to osteoporosis.

In individual cases, disturbances of liver function, some of them severe, have been reported with high dosed Cyproterone Sandoz 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 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

Common. Fatigue, hot flushes, sweating.

Very rare. Tiredness, sleep disturbances.

Cardiovascular

Very rare. Thrombotic phenomena, tachycardia.

Respiratory

Very rare. Shortness of breath.

Gastrointestinal

Very rare. Nausea and other gastrointestinal complaints.

Hepatobiliary

Common. Hepatic toxicity, including jaundice, hepatitis, hepatic failure

Rare. Jaundice, increased liver enzymes.

Very rare. Hepatitis, liver function disturbance, hepatic failure.

Reproductive system

Very common. Reversible inhibition of spermatogenesis.

Common. Gynaecomastia.

Very rare. Impaired spermatogenesis, breast tenderness, breast pain.

Skin

Uncommon. Rash.

Musculoskeletal and connective tissue disorders

Very rare. Osteoporosis.

Immune system disorders

Rare: Hypersensitivity reaction.

Metabolic and nutrition disorders

Common: Weight increased or weight decreased.

Psychiatric disorders

Very common. Libido decreased, erectile dysfunction.

Common. Depressed mood, restlessness (temporary).

Neoplasms benign and malignant

Very rare. Benign & malignant liver tumours

Respiratory, thoracic and mediastinal disorders

Common. Shortness of breath

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 Cyproterone Sandoz, 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 Sandoz doses of 25mg and above (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

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

Inoperable prostatic carcinoma

Suppression of “flare” with initial LHRH analogue therapy

Initially 100mg twice daily alone for 5-7 days, then 100mg twice daily for 3-4 weeks together with an LHRH agonist at the dosage recommended by the manufacturer.

Long-term palliative treatment without orchidectomy

100mg two or three times daily. Treatment should not be interrupted, nor the dosage reduced, after improvement or remissions have occurred.

Treatment of hot flushes (in patients treated with LHRH analogues or post-orchidectomy)

Low initial dose of 50mg once to three times daily, with upward titration to 100mg three times daily if necessary.

See PRECAUTIONS, ADVERSE EFFECTS and OVERDOSAGE.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

There is no experience in overdose and individual clinical assessment and symptomatic treatment is required immediately as appropriate.

Use of Cyproterone Sandoz 100mg at high doses has been associated with hepatic toxicity, particularly in the elderly (see ADVERSE EFFECTS).

PRESENTATION AND STORAGE CONDITIONS

Cyproterone Sandoz 100mg Tablets - white, scored tablets, marked 100 on one side.
Cyproterone Sandoz 100mg is available in blister packs of 50 tablets.

Store below 30 °C.

Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 15 November 2004

Date of most recent amendment: 18/02/2016