NAME OF THE MEDICINE

Cyproterone acetate.

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

Structural Formula:

![Structural Formula Image]

Molecular Formula: C_{24}H_{29}ClO_{4}

Molecular Weight: 416.94

Melting Point: 206 to 213°C

CAS Registry Number: 427-51-0

DESCRIPTION

Cyproterone acetate is a white to pale yellow crystalline powder. 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.

GenRx Cyproterone Acetate 100 mg Tablets are intended for oral administration. Each tablet contains cyproterone acetate 100 mg. In addition, each tablet contains the following inactive ingredients: Lactose, microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate.

PHARMACOLOGY

Pharmacological Actions

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 anti-androgenic 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 20 ng/mL (normal range 5–15 ng/mL) in studies of up to 6 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 100 mg oral and 300 mg intramuscular depot administration in 8 young women, and was found to be 80 ± 30% (range 23–199%). In a study to determine the bioequivalence of the GenRx Cyproterone Acetate 100 mg formulation in comparison to 100 mg cyproterone acetate tablets distributed by Schering Proprietary Ltd, the mean peak plasma concentration for cyproterone acetate from the GenRx Cyproterone Acetate formulation after administration of a single 100 mg dose, was 176.2 ng/mL at about 4 hours in comparison to 161.7 ng/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 5756.0 ng.h/mL for the GenRx Cyproterone Acetate 100 mg formulation versus 5953.3 ng.h/mL for 100 mg 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 3.5–4.0 % 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 15β-hydroxy cortisol acetate.

**Excretion**
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
- previous or existing hepatic tumours (only if these are not due to metastases from carcinoma of the prostate)
- Dubin-Johnson syndrome, Rotor syndrome
- presence or history of meningioma
- 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
- hypersensitivity to any of the components of GenRx Cyproterone Acetate 100 mg.

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 GenRx Cyproterone Acetate 100 mg is prescribed.

**PRECAUTIONS**

GenRx Cyproterone Acetate 100 mg is for use only in men.

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

In male patients long-term androgen deprivation with GenRx cyproterone acetate 100 mg may lead to osteoporosis.

**Thromboembolic events**

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 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 cyproterone acetate is prescribed.

**Liver**

The use of cyproterone acetate is contraindicated in patients with hepatic diseases.

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 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, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should be withdrawn, unless hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

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

**Meningioma**

The occurrence of meningiomas (single and multiple) has been reported in association with long-term use of cyproterone acetate at doses of 25mg/day and above. If a patient treated with cyproterone acetate is diagnosed with meningioma, treatment with cyproterone acetate 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 cyproterone acetate treatment (see CONTRAINDICATIONS). Carbohydrate metabolism should be monitored carefully.

Shortness of breath

A sensation of shortness of breath may occur in individual cases under high dose treatment with GenRx Cyproterone Acetate 100 mg. 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 preclinical data suggest a possible suppression due to the corticoid-like effect of cyproterone acetate with high doses.

Anaemia

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

Other conditions

GenRx Cyproterone Acetate 100 mg Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on Fertility

Spermatogenesis is impaired during treatment and recovers gradually after discontinuation (see PRECAUTIONS and ADVERSE EFFECTS).

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

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 Pregnancy (Category D)

GenRx Cyproterone Acetate 100 mg is for use only in men.

Use in the Elderly

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

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 GenRx Cyproterone Acetate. 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.

1 Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
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 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 2 mg/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.

Children and adolescents

Cyproterone acetate 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.

Cyproterone acetate must not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and the still unstabilised axes of endocrine function cannot be ruled out.

Patients with hepatic impairment

The use of cyproterone acetate is contraindicated in patients with liver diseases.

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 GenRx Cyproterone Acetate 100 mg 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.

At high therapeutic cyproterone acetate doses of three times 100mg per day, cyproterone acetate may inhibit CYP2C8 (see below). Thiazolidinediones (i.e. the anti-diabetics pioglitazone and rosiglitazone) are substrates or CYP2C8 (increased blood levels of these anti-diabetics may require dose adjustment).

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 inhibition 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 CYP 450 studies, the recommended clinical doses are likely to inhibit CYP 2C8, 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:

<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>
</tbody>
</table>
General
Very Common: tiredness, weight increase.
Common: headache, depressive moods.
Uncommon: sleep disturbances, hot flushes, allergic reactions.

Cardiovascular
Common: thrombotic phenomena.
Uncommon: tachycardia.

Respiratory
Rare: shortness of breath.

Gastrointestinal
Common: nausea and other gastrointestinal complaints.

Hepatobiliary
Rare: liver functions disturbance, hepatitis, jaundice, hepatic failure.

Musculoskeletal
Uncommon: osteoporosis.

Reproductive
Very Common: diminished libido, impaired spermatogenesis, inhibition of ovulation.
Common: mastodynia, gynaecomastia, breast tenderness, breast pain.
Uncommon: galactorrhoea, irregular menstrual cycles, dysmenorrhea, vaginal discharge, increased libido.

Skin
Uncommon: skin discolouration, striae.
Rare: rash.
Unknown Incidence: alteration in hair pattern.

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

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

Over the course of several weeks cyproterone acetate gradually impairs spermatogenesis as a result of the antiandrogenic and antigonadotropic actions. Spermatogenesis has taken 3 to 20 months to return to normal after discontinuing therapy.

Cyproterone acetate occasionally leads to gynaecomastia (sometimes combined with tenderness to touch of the breast).

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

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

Changes in body weight are possible.

Other adverse events reported at a low incidence are: skin discolouration, striae.
**Post-marketing Information**

The following adverse effects have been reported in users of cyproterone acetate (postmarketing data) but for which the association to cyproterone acetate 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 ≥ 1/10</th>
<th>Common ≥ 1/100 and &lt;1/10</th>
<th>Uncommon ≥ 1/1000 and &lt;1/100</th>
<th>Rare ≥ 1/10000 and &lt;1/1000</th>
<th>Very rare &lt;1/10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms benign and malignant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity reaction</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight increased or decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Libido decreased</td>
<td>Depressed mood</td>
<td>Restlessness (temporary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic toxicity, including jaundice, hepatitis, hepatic failure*</td>
<td>Increased liver enzymes</td>
<td>Liver function disturbance,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea GI complaints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Shortness of breath.*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Thrombotic phenomena Tachycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Reversible inhibition of spermatogenesis</td>
<td>Gynaecomastia</td>
<td>Breast tenderness Breast pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>System organ class (MedDRA)</td>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>≥ 1/10</td>
<td>≥ 1/100 and &lt;1/10</td>
<td>≥ 1/1000 and &lt;1/100</td>
<td>≥ 1/10000 and &lt;1/1000</td>
<td>&lt;1/10000</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue, Hot flushes, Sweating</td>
<td>Tiredness, Sleep disturbances, Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Blood and lymphatic system disorders**

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 acetate 100 mg, 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 of cyproterone acetate doses of 25mg and above (see CONTRAINDICATIONS and PRECAUTIONS).

* For further information see PRECAUTIONS
† A causal relationship with cyproterone acetate has not been established

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

**Long-Term Palliative Treatment Without Orchidectomy**
100 mg 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 50 mg once to three times daily, with upward titration to 100 mg three times daily if necessary (see PRECAUTIONS, ADVERSE EFFECTS and OVERDOSAGE).

**OVERDOSAGE**

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

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

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

**PRESENTATION AND STORAGE CONDITIONS**

**GenRx Cyproterone 100 mg Tablets:**
White to off-white, capsule-shaped tablet with ‘100’ engraved on one face, and a break line on the other face.

Blister packs of 50 tablets.

AUST R 101535.
* Not all strengths, pack types and/or pack sizes may be available.

**Storage**
Store below 30°C. Protect from light and moisture.

**POISONS SCHEDULE OF THE MEDICINE**
S4: Prescription Only Medicine

**NAME AND ADDRESS OF THE SPONSOR**
Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

GenRx is a registered trademark of Apotex Pty Ltd.

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):**
15 October 2008

**Date of most recent amendment:** 1st December 2011