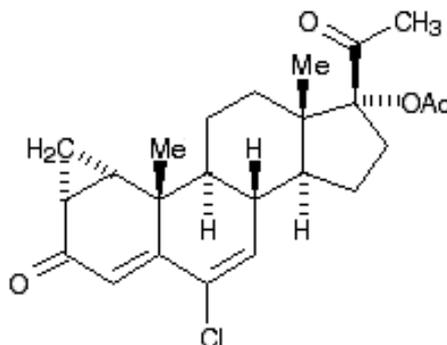


GenRx CYPROTERONE ACETATE 50 mg TABLETS**NAME OF THE MEDICINE**

Cyproterone acetate.

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

Structural Formula:

Molecular Formula: C₂₄H₂₉ClO₄

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 50 mg Tablets are intended for oral administration. Each tablet contains cyproterone acetate 50 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.

In women, hirsutism is diminished, but also androgen dependent loss of scalp hair and elevated sebaceous gland function are reduced. During the treatment ovarian function is inhibited.

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 $80 \pm 30\%$ (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 15 β -hydroxycyproterone 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

Women

Moderately Severe to Severe Signs of Androgenisation

- Moderately severe/severe forms of hirsutism
- moderately severe/severe androgen dependent loss of scalp hair (moderately severe/severe androgenic alopecia)
- moderately severe/severe forms of acne and/or seborrhoea associated with other features of androgenisation.

GenRx Cyproterone Acetate 50 mg inhibits the influence of male sex hormones which are also produced by the female. It is thus possible to treat diseases in women caused by either increased production of androgens or a particular sensitivity to these hormones. Hirsutism and alopecia may be expected to recur over a period of time after cessation of treatment.

If GenRx Cyproterone Acetate 50 mg is taken during pregnancy, the properties of the preparation may lead to signs of feminisation in the male fetus. Therefore, in women of childbearing potential, pregnancy must be excluded at the commencement of treatment and ethinyloestradiol taken as well to ensure contraception. This also promotes regular menstruation.

Men

Reduction of Drive in Sexual Deviations

GenRx Cyproterone Acetate 50 mg reduces the force of the sexual urge in men with sexual deviations. Whilst under treatment the man can control himself better in a predisposing stimulatory situation, but there is no influence on any deviating direction of sexual drive. Abnormal patterns of sexual behaviour require treatment when they are distressing to the patient. A pre-requisite for therapy is the desire by the patient for treatment.

GenRx Cyproterone Acetate 50 mg should be supplemented by psychotherapeutic and sociotherapeutic measures in order to exploit the period of reduced drive for personal and social reorientation.

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

Contraindications in women

- Pregnancy
- lactation
- hepatic diseases
- previous or existing hepatic tumours (only if these are not due to metastases due to carcinoma of the prostate)
- history of jaundice or persistent itching during a previous pregnancy
- history of herpes of pregnancy
- Dubin-Johnson syndrome, Rotor syndrome
- presence or history of meningioma
- wasting diseases
- 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 50 mg.

When cyproterone is used together with a progestogen-oestrogen-containing preparation for cyclical combined therapy of severe signs of androgenisation, the prescriber and patients should also be aware of the contraindications contained in the product information for the progestogen-oestrogen containing preparation.

Reduction of drive in sexual deviations

- Hepatic diseases
- Dubin-Johnson syndrome, Rotor syndrome
- previous or existing hepatic tumours (see also Contraindications in inoperable carcinoma of the prostate)
- presence or history of meningioma
- wasting diseases
- 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 50 mg.

Inoperable carcinoma of the prostate

- Hepatic 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 carcinoma of the prostate)
- severe chronic depression
- previous or existing thromboembolic processes
- hypersensitivity to any of the components of GenRx Cyproterone Acetate 50 mg.

In patients with prostatic carcinoma presenting 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 50 mg is prescribed.

GenRx Cyproterone Acetate 50 mg should not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and the still unestablished axes of endocrine function cannot be ruled out.

PRECAUTIONS

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

Thromboembolic events

The occurrence of thromboembolic events has been reported in patients using cyproterone acetate, 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 inoperable carcinoma of the prostate presenting 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 pre-treatment, 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 50 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 50 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.

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

Combined Cyproterone Acetate / Oestrogen Therapy (see also **DOSAGE AND ADMINISTRATION**, Women of Childbearing Potential).

With the additional use of a combined oral contraceptive preparation, refer to the Product Information for that product. The following additional information is applicable to use of all cyclic combined oestrogen-progestogen therapies, including oral contraceptives.

Use of combined oestrogen-progestogen medication may be associated with an increased risk of thromboembolism, stroke and myocardial infarction, increasing over the age of 30 years and further increased by cigarette smoking, hypertension, obesity, diabetes, hypercholesterolaemia or a history of pre-eclamptic toxemia. The risk of myocardial infarction is substantially increased in women aged 40 years and over. All users of combined oestrogen-progestogen medications should be encouraged not to smoke.

Therapy should be discontinued if feasible at least six weeks prior to elective surgery of a kind associated with increased risk of embolism and during any period of prolonged immobilisation. Optic neuritis and retinal thrombosis have been reported in association with combined oestrogen-progestogen treatment. Discontinue medication pending examination if there is unexplained sudden partial or complete loss of vision, sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema or retinal vascular lesions, medication should be withdrawn.

Susceptible women may experience a rise in blood pressure. The prevalence of hypertension increases with the duration of use and the age of the patient. Blood pressure should be measured and care should

be exercised in prescribing these preparations for patients with hypertension. Regular monitoring of blood pressure is desirable.

The first spontaneous ovulation after stopping combined oestrogen-progestogen treatment is sometimes delayed; and there is evidence of temporary impairment of fertility in some women who discontinue combined oestrogen-progestogen treatment which appears to be independent of the duration of use. Impairment diminishes with time, but may be evident up to 30 months after cessation in nulliparous women. It should be suggested to patients who decide to become pregnant that alternative methods of contraception be used until they have their first spontaneous period, so that the estimated date of delivery may be made with more certainty.

Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease or abnormal mammographs, should be monitored with particular care after they elect to use combined oestrogen-progestogen treatment.

Epidemiological studies report doubling of the risk of gall bladder disease in women who have used combined oestrogen-progestogen treatment for two or more years. The onset or exacerbation of migraine or other persistent severe headache requires discontinuation of combined oestrogen-progestogen treatment pending full investigation.

Contraceptive efficacy may be impaired by drug interactions, especially rifampicin, semisynthetic penicillins and anticonvulsant drugs, and also by severe diarrhoea, or by vomiting shortly after the ingestion of a tablet.

Before prescribing combined oestrogen-progestogen treatment, a complete history and physical examination should be undertaken, with particular reference to blood pressure, breasts, abdomen and pelvic organs. A Papanicolaou smear and urinalysis should be carried out.

Combined oestrogen-progestogen treatment may cause some degree of fluid retention. Care is therefore necessary in those diseases which may be aggravated, especially cardiac and renal insufficiency, migraine and asthma. Patients should be warned that vulvovaginal monilial infection may occur or recur, and of the need for appropriate treatment.

Pyridoxine and folate plasma levels may be depressed by combined oestrogen-progestogen treatment. Folate supplementation may be desirable if a patient becomes pregnant shortly after ceasing tablet taking.

Certain changes may be induced in laboratory data as follows. Liver function tests: transaminases (AST, ALT) and bromsulphthalein retention are increased.

Clotting factors VII, VIII, IX and X, prothrombin and platelet aggregation are increased, but antithrombin III decreased.

Thyroid function tests: Thyroid binding globulin (TBG), Total thyroxine (T_4), and protein bound iodine (PBI) are increased. T_3 resin uptake (reflecting TBG) is decreased, whilst free T_4 and clinical thyroid state remain unaltered.

Adrenal function: plasma cortisol is increased (due to increase in steroid binding globulins) whilst adrenal function is essentially normal.

Agglutination reactions: false positive rheumatoid factor and antinuclear factor are increased.

Blood glucose, phospholipids and triglycerides are increased. These tests usually return to pre-therapy values shortly after discontinuation of oestrogen-progestogen treatment.

Specifically to be observed in women

Before the start of therapy a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out. Serious organic causes of androgenisation, e.g. Cushing's syndrome, ovarian tumours, adrenal carcinoma and adrenogenital syndrome should be excluded. Pregnancy must be excluded at the time of commencing treatment in women of childbearing potential.

If, during combined treatment, spotting occurs during the three weeks in which the tablets are being taken, tablet taking should not be interrupted. However, if persistent, recurrent or heavy bleeding occurs at irregular intervals, a gynaecological examination must be carried out to exclude organic disease.

With regard to the additional use of a combined oral contraceptive preparation, attention is drawn to all the data contained in the product information for this product.

Specifically to be observed in men

The sexual drive reduction effect of GenRx Cyproterone Acetate 50 mg can be diminished under the disinhibitory influence of alcohol.

In patients with inoperable carcinoma of the prostate presenting 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.

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 D¹)

The use of GenRx Cyproterone Acetate 50 mg is contraindicated during pregnancy (also see **CONTRAINDICATIONS**).

Administration of cyproterone acetate during the hormone-sensitive differentiation stage of the genital organs (after approx. day 45 of pregnancy) could lead to signs of feminisation in the male foetus.

Use in Lactation

The use of GenRx Cyproterone Acetate 50 mg is contraindicated during lactation, as small amounts of cyproterone acetate are excreted in breast milk.

Children and adolescents

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

Cyproterone acetate is not recommended for use in female patients before the conclusion of puberty.

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.

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 50 mg.

Patients with hepatic impairment

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

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.

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 50 mg. *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.

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.

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 50 mg 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 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 of CYP2C8 (increased blood levels of these anti-diabetics may require dose adjustment).

Contraceptive efficacy may be impaired by drug interactions especially anticonvulsant drugs, penicillins and rifampicin (antibiotics).

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 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:

| | |
|---------------|-------------------------|
| Very common - | ≥ 1/10 |
| Common - | ≥ 1/100 and < 1/10 |
| Uncommon - | ≥ 1/1000 and < 1/100 |
| Rare - | ≥ 1/10,000 and < 1/1000 |
| Very rare - | < 1/10,000 |

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, irregular menstrual cycles, gynaecomastia, breast tenderness, breast pain. |
| Uncommon: | galactorrhoea, dysmenorrhoea, vaginal discharge, increased libido. |

Skin

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

The most commonly reported adverse drug reactions (ADRs) in female patients receiving cyproterone acetate are spotting, weight increase and depressed mood.

The most frequently observed ADRs in male 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.

In male patients cyproterone acetate occasionally leads to gynaecomastia (sometimes combined with tenderness to touch of the breast).

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

In women ovulation is inhibited under the combined treatment so that a state of infertility exists.

A feeling of tension in the breasts may occur.

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 were dysmenorrhoea, vaginal discharge, skin discolouration, striae.

Postmarketing Information

The following adverse effects have been reported in users of cyproterone acetate and are based on postmarketing data and cumulative experience. 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 & malignant liver tumours* |
| Immune system disorders | | | | Hypersensitivity reaction | |
| Metabolism and nutrition disorders | | Weight increased or Weight decreased | | | |
| Psychiatric disorders | Libido decreased (men), Erectile dysfunction | Depressed mood Restlessness (temporary) | Libido decreased (women) | Libido increased (women) | |
| Skin and subcutaneous tissue disorders | | | Rash | | |
| Musculoskeletal and connective tissue disorders | | | | | Osteoporosis (men) |

| 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 |
|---|---|---|------------------------------------|----------------------------------|---|
| Hepatobiliary disorders | | Hepatic toxicity, including jaundice, hepatitis, hepatic failure* | | Increased liver enzymes | Liver function disturbance |
| Gastrointestinal disorders | | | | | Nausea GI complaints |
| Cardiovascular disorders | | | | | Thrombotic phenomena Tachycardia |
| Reproductive system and breast disorders | Reversible inhibition of spermatogenesis Ovulation inhibited | Gynaecomastia (men) Breast tenderness (women) | | | Diminished libido, increased libido, impaired spermatogenesis, gynaecomastia, breast tenderness, breast pain, irregular menstrual periods, galactorrhoea. |
| General disorders and administration site conditions | | Fatigue Hot flushes Sweating | | Hypochromic anaemia | Tiredness sleep disturbances, headache, allergic reactions |
| Respiratory, thoracic and mediastinal disorders | | Shortness of breath* | | | |

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*†.

In male patients under treatment with cyproterone acetate, 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.

Women

Women of Childbearing Potential

Pregnant women must not take GenRx Cyproterone Acetate 50 mg, therefore pregnancy must be excluded at the time therapy is commenced in women of childbearing potential. In women of childbearing potential, the treatment is commenced on the fifth day of the cycle (first day of bleeding = first day of the cycle). Only women with amenorrhoea or menstrual bleeding at very irregular intervals can start treatment immediately. In this case the first day of treatment is to be regarded as the fifth day of the cycle and the following recommendations then observed.

Hirsutism Secondary to Female Androgenisation

The usual starting dose is one 50 mg tablet taken daily for ten days per month (from the fifth to the 14th day of the cycle). Once a satisfactory response has been attained it is usually possible to reduce the dose further. Doses as low as 10 mg/day for ten days per month have been shown to be adequate for maintenance therapy in this condition.

Other Severe Signs of Androgenisation

Two 50 mg tablets daily for ten days per month (from the fifth to the 14th day of the cycle). Take with some liquid after a meal.

Following clinical improvement, the daily dose may be reduced to one or half a tablet during the ten days on which it is given in each treatment cycle. The dose regimen for ethinyloestradiol (see **PRECAUTIONS**, Combined Cyproterone Acetate / Oestrogen Therapy, below) remains unchanged. If improvement is maintained over a further few months, cyproterone acetate 10 mg daily for 15 days per month (from the fifth to the 19th day of the cycle) may be sufficient.

Combined Cyproterone Acetate / Oestrogen Therapy

In addition to GenRx Cyproterone Acetate 50 mg, women of child-bearing potential should receive a combined oral contraceptive, containing oestrogen, daily from the fifth to the 25th day of the cycle to provide the necessary contraceptive protection and to stabilise the cycle (refer to the full Product Information document for the chosen combined oral contraceptive preparation).

Women receiving the cyclical combined therapy should take their tablets at the same time each day. If a tablet is missed and if more than 12 hours elapse from this time i.e. more than 36 hours have elapsed since the last tablets were taken), contraceptive protection in this cycle may be reduced. The use of GenRx Cyproterone Acetate and a combined oral contraceptive containing low dose oestrogen should nevertheless be continued according to the instructions, ignoring the missed tablet or tablets, in order to avoid premature bleeding in this cycle. However, an additional non-hormonal barrier method of contraception (not the rhythm or temperature methods) is to be employed for the rest of the cycle.

A seven day tablet free interval is observed after 21 days, during which time a withdrawal bleeding occurs.

Exactly four weeks after the first course of treatment was started, i.e. on the same day of the week, the next cyclical course of combined treatment is started, regardless of whether bleeding has stopped or not. If no bleeding occurs during the tablet free interval, the possibility of pregnancy must be excluded before restarting tablet taking.

As the dose of cyproterone acetate is reduced, contraceptive efficacy may be impaired. Therefore, a reliable form of contraception (not the rhythm or temperature methods) must be employed during treatment. If a non-hormonal method is adopted, a combined oral contraceptive containing low dose oestrogen from day five to 25 will need to be continued to stabilise the cycle (see also **PRECAUTIONS**, Combined Cyproterone Acetate / Oestrogen Therapy).

Post-Menopausal and Hysterectomised Women

In post-menopausal or hysterectomised patients, GenRx Cyproterone Acetate 50 mg may be administered alone. According to the severity of the complaints, the average dose should be half to one tablet (25 to 50 mg) once daily for 21 days, followed by a seven day tablet free interval.

Duration of Treatment

The duration of treatment depends on the severity of the pathological signs of androgenisation and response to treatment. Treatment is usually carried out over several months initially. Acne and

seborrhoea usually respond sooner than hirsutism or alopecia. Hirsutism and alopecia are likely to recur when treatment is stopped.

Men

Reduction of Drive in Sexual Deviation

The individual dose will be determined by the response. Generally, treatment is started with one 50 mg tablet twice daily. It may be necessary to increase the dose to two 50 mg tablets twice daily, or even two 50 mg tablets three times daily for a short period of time. If a satisfactory result is achieved, the therapeutic effect should be maintained with the lowest possible dose. Quite often half a tablet twice daily is sufficient. When establishing the maintenance dose or when discontinuing the preparation, the dosage should not be reduced abruptly, but gradually. To this end, the daily dose should be reduced by one tablet, or better, by half a tablet, at intervals of several weeks.

To stabilise the therapeutic effect it is necessary to take GenRx Cyproterone Acetate 50 mg over a protracted period of time, if possible with the simultaneous use of psychotherapeutic measures.

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 50 mg at high doses has been associated with hepatic toxicity, particularly in the elderly (see **ADVERSE EFFECTS**).

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

PRESENTATION AND STORAGE CONDITIONS

GenRx Cyproterone 50 mg Tablets

White, round, flat tablet marked 50 with a scoreline on one face, plain on the other.

Bottles of 20 and 50 tablets.

AUST R 101534.

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

Store below 30°C. Protect from light and moisture

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.

POISONS SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine

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

15 October 2008

Date of most recent amendment: 1st December 2011