

AUSTRALIAN PRODUCT INFORMATION – APO-CYPROTERONE ACETATE 50MG TABLETS (CYPROTERONE ACETATE)

1 NAME OF THE MEDICINE

Cyproterone acetate

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

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.

APO-Cyproterone Acetate 50 mg Tablets are intended for oral administration.

The tablets are white, round, flat marked 50 with a scoreline on one face, plain on the other. Each tablet contains 50 mg cyproterone acetate as the active ingredient. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

APO-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 APO-Cyproterone Acetate 50 mg is taken during pregnancy, the properties of the preparation may lead to signs of feminisation in the male foetus. 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

APO-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.

APO-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.

4.2 DOSE AND METHOD OF ADMINISTRATION

The tablets are to be taken with some liquid after a meal.

Women

Pregnant women must not take APO-Cyproterone Acetate 50 mg, therefore pregnancy must be excluded before the start of therapy.

In women of childbearing potential, the treatment is commenced on the first day of the cycle (= 1st day of bleeding). 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 first day of the cycle and the following recommendations then observed as normal.

For hirsutism secondary to female androgenisation; the usual starting dose should be one 50 mg tablet taken daily for ten days per month (from the 1st to the 10th 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.

For other severe signs of androgenisation; two 50 mg tablets are to be taken daily from the 1st to the 10th day of the cycle (= for 10 days).

In addition, these women should receive a progestogen-oestrogen containing preparation, to provide the necessary contraceptive protection and to stabilise the cycle. An appropriate combined oral contraceptive preparation should be commenced on day 1 of the cycle as directed.

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, contraceptive protection in this cycle may be reduced. **Attention is drawn to the special notes (especially on contraceptive reliability and to the missed tablet recommendations) in the product information for the combined oral contraceptive preparation being taken in conjunction with APO-Cyproterone Acetate 50 mg.** If bleeding fails to occur after this cycle, pregnancy must be excluded before tablet-taking is resumed.

Missed APO-Cyproterone Acetate 50 mg tablets may diminish the therapeutic efficacy and may lead to intermenstrual bleeding. The missed APO-Cyproterone Acetate 50mg tablet should be disregarded (no double dose should be taken to make up for the missed tablet) and tablet taking resumed at the regular time together with the combined oral contraceptive preparation.

A withdrawal bleeding usually occurs during the tablet free interval or whilst taking the 7-day placebo tablets. 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.

Following clinical improvement, the daily dose of APO-Cyproterone Acetate 50 mg may be reduced to 1 or ½ a tablet during the 10 days on which it is given in each treatment cycle. The dose regimen for the combined oral contraceptive preparation remains unchanged. If improvement is maintained over a further few months, cyproterone acetate 10 mg daily from the 1st to the 15th day of the cycle (= 15 days) may be sufficient.

In postmenopausal or hysterectomised patients APO-Cyproterone Acetate 50mg may be administered alone. According to the severity of the complaints, the average dose should be 1/2 to 1 tablet APO-Cyproterone Acetate 50mg once daily for 21 days, followed by a 7-day tablet-free interval.

The length 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

The maximum daily dose is 300 mg.

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 1/2 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 1/2 a tablet, at intervals of several weeks.

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

Inoperable Prostatic Carcinoma

- To reduce the initial increase of male sex hormones ('flare') in treatment with LHRH agonists:
Initially 100 mg (2 tablets of Cyproterone Acetate 50mg) twice daily alone for 5–7 days, then 100 mg (2 tablets of Cyproterone Acetate 50mg) twice daily for 3–4 weeks together with an LHRH agonist at the dosage recommended by the manufacturer.
- In long term palliative treatment of advanced prostate cancer in patients who have not had an orchiectomy:
100 mg (2 tablets of Cyproterone Acetate 50mg) 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 LHRH analogues or who have had orchiectomy:
50 mg once to three times daily, with upward titration to 100 mg three times daily if necessary.

Children and Adolescents

Cyproterone Acetate is not recommended for use in female patients before conclusion of puberty. There are no data suggesting the need for dosage adjustment in female patients who have completed 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.

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.

Use in the Elderly

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

Patients with Hepatic Impairment

The use of Cyproterone Acetate 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.

4.3 CONTRAINDICATIONS

Contraindications in women

- Pregnancy
- Lactation
- Hepatic diseases
- Dubin-Johnson syndrome, Rotor syndrome
- History of jaundice or persistent itching during a previous pregnancy
- History of herpes of pregnancy
- Previous or existing hepatic tumours
- 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 APO-Cyproterone Acetate 50 mg.

With regard to the cyclical combined therapy of severe signs of androgenisation, attention is also drawn to the data on contraindications contained in the product information for the progestogen-oestrogen containing preparation used in addition to Cyproterone Acetate 50 mg.

Contraindications in men

Reduction of drive in sexual deviations

- Hepatic diseases
- Dubin-Johnson syndrome, Rotor syndrome
- Previous or existing hepatic tumours
- 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 APO-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 inoperable carcinoma of the prostate)
- Severe chronic depression
- Existing thromboembolic processes
- Hypersensitivity to any of the components of APO-Cyproterone Acetate 50 mg.

APO-Cyproterone Acetate 50 mg should 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

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

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.

Liver

Liver function tests should be performed pre-treatment, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur.

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 fatal cases were in men with prostatic cancer. Toxicity is dose related and usually develops several months after treatment has begun. 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.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with long-term use (years) of cyproterone acetate at doses of 25 mg/day and above. If a patient treated with cyproterone acetate is diagnosed with meningioma, treatment with cyproterone acetate must be stopped (see 4.3-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 4.3-Contraindications).

Shortness of Breath

A sensation of shortness of breath may occur in individual cases under high dose treatment with APO-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

APO-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.

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 or recurrent bleeding occurs at irregular intervals, a gynaecological examination must be carried out to exclude organic diseases.

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 APO-Cyproterone Acetate 50 mg can be diminished under the 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.

Use in the Elderly

There is reduced hepatic clearance in the elderly, and this should be considered when prescribing and monitoring treatment with APO-Cyproterone Acetate 50 mg.

Paediatric Use

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.

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.

Effects on laboratory tests

Currently, there are no available data regarding the effects on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The requirement for oral anti-diabetics 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, 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 co-administered 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 3 times 100 mg per day.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

Spermatogenesis is impaired during treatment and recovers gradually after discontinuation of therapy (see 4.8-Adverse effects (undesirable 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 3-20 months to return to normal after discontinuing therapy.

Use in Pregnancy (Category D)

The use of APO-Cyproterone Acetate 50 mg is contraindicated during pregnancy (also 4.3-Contraindications).

Administration of cyproterone acetate during the hormone-sensitive differentiation phase 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 APO-Cyproterone Acetate 50 mg is contraindicated during lactation, as small amounts of cyproterone acetate are excreted in human milk (see 4.3-Contraindications).

4.7 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 APO-Cyproterone Acetate 50 mg can lead to tiredness and diminished vitality and can impair the ability to concentrate.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

Cardiovascular

Common:	thrombotic phenomena.
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Gastrointestinal

Common: nausea and other gastrointestinal complaints.

Reproductive

Very common: diminished libido.

Common: mastodynia, irregular menstrual cycles.

Skin

Rare: rash

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 recovers gradually within several months of discontinuing therapy.

In male patients cyproterone acetate 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.

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.

Post Marketing Information

The following adverse effects have been reported in users of cyproterone acetate and are based on post-marketing data and cumulative experience with cyproterone acetate. 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 1: The adverse events reported in users of cyproterone acetate based on post-marketing data and cumulative experience with cyproterone acetate.

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				Hyper-sensitivity 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)
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)			Breast pain Irregular menstrual periods Galactorrhoea.
General disorders and administration site conditions		Fatigue Hot flushes Sweating			Tiredness Sleep disturbances Headache

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
Respiratory, thoracic and mediastinal disorders		Shortness of breath*			

* For further information see 4.4-Special warnings and precautions for use.

The ADRs identified only during post-marketing surveillance and for which a frequency could not be estimated are: anaemia*, meningioma, intra-abdominal haemorrhage*, rash, menstrual spotting*, 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 25 mg and above (see 4.3-Contraindications and 4.4-Special warnings and precautions for use).

* For further information see 4.4-Special warnings and precautions for use.

† A causal relationship with cyproterone acetate has not been established.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Cyproterone acetate is an anti-androgenic hormone.

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 exerts a direct anti-androgenic action on the tumour and its metastases.

Cyproterone acetate in addition has a progestogenic action exerting a negative feedback effect on the hypothalamic receptors, so leading to a reduction in gonadotropin release, and

hence to diminished production of testicular androgens. Treatment with cyproterone acetate in men results in a reduction of sexual drive and potency and inhibition of gonadal function. These changes are reversible following discontinuation of the therapy.

The antigonadotropic effect of cyproterone acetate is also exerted when the substance is combined with luteinising hormone releasing hormone (LHRH) agonists. The initial increase of testosterone provoked by this substance group is decreased by cyproterone acetate.

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.

Prolactin levels may increase with higher doses of cyproterone acetate. Studies showed increased prolactin levels up to 20 ng/mL (normal range 5–15 ng/mL). There are no data for periods longer than 6 months.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

The ingestion of 50mg of cyproterone acetate gives maximum serum levels of about 140ng/mL at about 3 hours. Thereafter, drug serum levels declined during a time interval of typically 24 to 120 hours, with a terminal half-life of 43.9 ± 12.8 hours. The total clearance of cyproterone acetate from serum was determined to be 3.5 ± 1.5 mL/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 100 mg oral and 300 mg intramuscular depot administration and was found to be $80 \pm 30\%$ 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 2 mg cyproterone acetate in combination with 35 µg ethinyloestradiol, the free fraction of cyproterone acetate was about 3.5–4.0%. 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 1 metabolism of cyproterone acetate is mainly catalysed by the cytochrome P450 enzyme CYP3A4.

Excretion

In a study in 6 women administered a ¹⁴C labelled dose of 2 mg cyproterone acetate in combination with 50 µg 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

Due 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 cyproterone acetate. 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.

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 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 2 mg/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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See Section 4.5-Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

Bottles (white HDPE with PP cap):

- 20 tablets (AUST R 101534)
- 50 tablets (AUST R 101534)

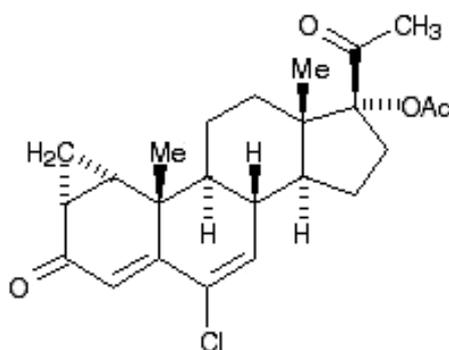
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Structural Formula:



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

Molecular Formula: C₂₄H₂₉ClO₄

Molecular Weight: 416.94

CAS number

427-51-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Apotex Pty Ltd

16 Giffnock Avenue

Macquarie Park NSW 2113

Australia

Tel: +61 2 8877 8333

Web: www1.apotex.com/au

9 DATE OF FIRST APPROVAL

22 June 2004

10 DATE OF REVISION

2 July 2018

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information
All	Trade name changed from GenRx to APO.