AUSTRALIAN PRODUCT INFORMATION

CYPRONE 50

Cyproterone acetate tablets

1 NAME OF THE MEDICINE

Cyproterone acetate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Cyprone 50 tablet contains 50 mg of cyproterone acetate as the active ingredient.

Excipients with known effect: Contains sugars (as lactose).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Cyprone 50	:	White circular flat bevelled tablets, with breakline on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Women

Moderately severe to severe signs of androgenization

- moderately severe/severe forms of hirsutism
- moderately severe/severe androgen-dependent loss of scalp hair (moderately severe/severe androgenetic alopecia)
- moderately severe/severe forms of acne and/or seborrhoea associated with other features of androgenization

Cyproterone acetate inhibits the influence of male sex hormones which are also produced by the female. It is thus possible to treat diseases in women caused either by 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 Cyprone 50 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 ethinylestradiol taken as well to ensure contraception. This also promotes regular menstruation.

Men

Reduction of drive in sexual deviations

Cyprone 50 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 prerequisite for therapy is the desire by the patient for treatment.

Cyprone 50 therapy should be supplemented by psychotherapeutic and sociotherapeutic measures in order to exploit the period of reduced drive for personal and social re-orientation.

Inoperable prostatic carcinoma

- to suppress "flare" with initial LHRH analogue therapy
- in long-term *palliative* treatment where LHRH analogues or surgery are ineffective, not tolerated, contraindicated or where oral therapy is preferred
- In the treatment of hot flushes in patients treated with LHRH analogues or who *have* had orchidectomy

4.2 DOSE AND METHOD OF ADMINISTRATION

Cyprone 50 tablets are to be taken with some liquid after a meal.

Women

Pregnant women must not take Cyprone 50. Therefore, pregnancy must be excluded before the start of therapy.

In women of child bearing potential, the treatment is commenced on the 1st 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 1st day of the cycle and the following recommendations then observed as normal.

For hirsutism secondary to female androgenization, the usual starting dose should be one tablet of Cyprone 50 taken daily for 10 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 a day for 10 days per month have been shown to be adequate for maintenance therapy in this condition.

For other severe signs of androgenization, 2 tablets of Cyprone 50 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 keep to a particular time of the day for tablet taking. 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 Cyprone 50.** If bleeding fails to occur after this cycle, pregnancy must be excluded before tablet-taking is resumed.

Missed Cyprone 50 tablets may diminish the therapeutic efficacy and may lead to intermenstrual bleeding. The missed Cyprone 50 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 4 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 or 7 day placebo tablet interval, the possibility of pregnancy must be excluded before restarting tablet taking.

Following clinical improvement, the daily dose of Cyprone 50 may be reduced to 1 or ½ 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. Re-evaluate the treatment with Cyprone 50 at the start of the menopause. Long-term use (years) of Cyprone 50 should be avoided (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Meningioma).

In postmenopausal or hysterectomised patients Cyprone 50 may be administered alone. According to the severity of the complaints, the average dose should be ½ to 1 tablet Cyprone 50 once daily for 21 days, followed by a 7 day tablet-free interval.

The length of the 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 in the drive of 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. The duration of cyproterone acetate treatment should be defined on an individual basis. If a satisfactory result is achieved, the therapeutic effect should be maintained with the lowest possible dose. Quite often ½ 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 1 tablet, or better ½ tablet, at intervals of several weeks.

To stabilise the therapeutic effect it is necessary to take Cyprone 50 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 LH-RH agonists

Initially 100 mg (2 tablets Cyprone 50) twice daily alone for 5-7 days, then 100 mg (2 tablets Cyprone 50) twice daily for 3-4 weeks together with an LHRH agonist in the dosage recommended by the manufacturer.

In long term palliative treatment of advanced prostate cancer in patients who have not had an orchidectomy

100 mg (2 tablets Cyprone 50) 2 to 3 times daily. Treatment should not be interrupted nor the dosage reduced after improvement or remissions have occurred.

To treat hot flushes in patients under treatment with LH-RH analogues or who have had orchiectomy

50 mg once to three times daily with upward titration to 100 mg three times daily if necessary.

Paediatric use Cyproterone 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 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 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 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
- Liver diseases
- Dubin-Johnson syndrome, Rotor syndrome
- History of jaundice or persistent pruritus during a previous pregnancy
- History of herpes of pregnancy
- Previous or existing liver 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 Cyprone 50

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 Cyprone 50.

Contraindications in men

Reduction of drive in sexual deviations

- Liver diseases
- Dubin-Johnson syndrome, Rotor syndrome
- Previous or existing liver 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 Cyprone 50

Inoperable carcinoma of the prostate

- Liver diseases
- Dubin-Johnson syndrome, Rotor syndrome

- Previous or existing liver tumours (only if these are not due to metastases from carcinoma of the prostate)
- Presence or history of meningioma
- Wasting diseases (with the exception of inoperable carcinoma of the prostate)
- Severe chronic depression
- Existing thromboembolic processes
- Hypersensitivity to any of the components of Cyprone 50

Cyprone 50 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

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

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 3-20 months to return to normal after discontinuing therapy.

As with other antiandrogenic treatments, in male patients long-term androgen deprivation with Cyprone 50 may lead to osteoporosis.

Liver

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 advanced carcinoma of the prostate. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone should normally 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 liver tumours, which may lead to life-threatening *intra-abdominal* haemorrhage, have been observed after the use of hormonal steroids. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnostic considerations.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with long-term use (years) of cyproterone at doses of 25 mg/day and above. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate. If a patient treated with Cyprone 50 is diagnosed with meningioma, treatment with cyproterone containing products, including Cyprone 50 must be permanently stopped (see Section 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 Cyprone 50 treatment (see Section 4.3 CONTRAINDICATIONS).

Shortness of breath

A sensation of shortness of breath may occur in individual cases under high-dose treatment with Cyprone 50. 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.

Thromboembolic events

The occurrence of thromboembolic events has been reported in patients using Cyprone 50 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.

Adrenocortical function

During treatment adrenocortical function should be checked regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of Cyprone 50 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

Cyprone 50 tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose mal absorption 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 child-bearing potential. If, during the combined treatment, spotting occurs during the 3 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-reducing effect of Cyprone 50 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 Cyprone 50 is prescribed.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric Use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The requirement for oral antidiabetics or insulin can change.

Although clinical interaction studies have not been performed, since this drug is metabolized by CYP3A4, it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4 inhibit the metabolism of cyproterone acetate. On the other hand, inducers of CYP3A4 such as e.g. rifampicin, phenytoin and products containing St. John´s wort may reduce the levels of cyproterone acetate.

The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMGCoA inhibitors (statins), which are primarily metabolised by CYP3A4, are co- administered with high therapeutic cyproterone acetate doses since they share the same metabolic pathway.

Based on *in vitro* CYP450 studies, the recommended clinical doses are likely to inhibit CYP2C8, and an inhibition of the CYP 2C9, 2C19, 3A4, and 2D6 is also possible at high therapeutic cyproterone acetate doses of 3 times 100 mg per day.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.1 PHARMACODYNAMIC PROPERTIES.

Use in Pregnancy

Pregnancy Category: D

The use of Cyprone 50 is contraindicated during pregnancy (also see Section 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 male fetuses.

Use in Lactation

The use of Cyprone 50 is contraindicated during lactation as small amounts of cyproterone acetate are excreted in breast milk (see Section 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 Cyprone 50 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	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000

Very rare <1/10,000

General

Very common: tiredness, weight increase

Common: headache, depressive moods

Cardiovascular

Common: thrombotic phenomena

Gastrointestinal

Common: nausea and other gastrointestinal complaints

Reproductive

Very common: diminished libido

Common: mastodynia, 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 discontinuation of treatment or reduction of the dose.

As with other antiandrogenic treatments, 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.

Post-marketing information

The following adverse effects have been reported in users of cyproterone acetate. The most appropriate MeDRA 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*
Blood and lymphatic system disorders					
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)
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
Respiratory, thoracic and mediastinal disorders		Shortness of breath*			

* For further information see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.
† A causal relationship with Cyprone 50 has not been established.

The ADRs identified only during post-marketing surveillance and for which a frequency could not be estimated are: anaemia*, meningioma, intra-abdominal haemorrhage*, rash, menstrual spotting*, thromboembolic events*†.

In male patients under treatment with Cyprone 50, sexual drive and potency are reduced and gonadal function is inhibited. These changes are reversible after discontinuation of therapy.

Meningiomas have been reported in association with long-term use (several years) of Cyprone 50 doses of 25 mg and above (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Cyprone 50 is an antiandrogenic hormone preparation.

Cyproterone acetate inhibits 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, Cyprone 50 therefore exerts a direct antiandrogenic action on the tumour and its metastases.

Cyproterone acetate in addition has a progestogenic action exerting a negative feedback effect centrally on the hypothalamic receptors, so leading to a reduction in gonadotropin release, and hence to diminished production of testicular androgens. Treatment with cyproterone acetate in men results in a reduction of sexual drive and potency and inhibition of gonadal function. These changes are reversible following discontinuation of the therapy.

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

acetate. 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 can increase slightly under 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 50 mg of cyproterone acetate gives maximum serum levels of about 140 ng/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 ± 12.8h. 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 ± 30% when averaged over all volunteers (range 23% to 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 ethinylestradiol, the free fraction of cyproterone acetate was about 3.5-4%. Because protein binding is non- specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

Metabolism

Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15ß-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

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, an accumulation of cyproterone acetate by a factor of about 3 can be expected in the serum during repeated daily administration.

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) and also in freshly isolated rat and human hepatocytes. This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimes for

cyproterone acetate. *In vivo* consequence 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 uncertain.

Carcinogenicity

Long-term animal carcinogenicity studies were performed in rats and mice. In one rat study, an increased incidence of tumours was reported at oral dose levels of 50 mg/kg cyproterone acetate and above (the tumours were diagnosed as hepatomas). 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 dosed 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

Cyprone 50 contains the following excipients: lactose monohydrate, maize starch, povidone, magnesium stearate, colloidal anhydrous silica and pregelatinised maize starch.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al foil blisters

Pack sizes: Each pack contains 20 or 50 tablets

Some pack sizes may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

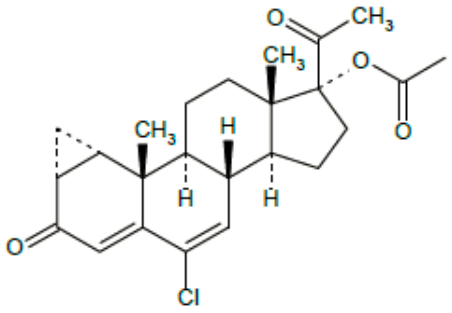
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

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

Structural formula :



Molecular formula : $C_{24}H_{29}ClO_4$ Molecular weight : 416.95

CAS Number

427-51-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

1 June 2016

10 DATE OF REVISION

04/02/2021

Summary Table of Changes

Section Changed	Summary of New Information
4.2; 4.4; 4.6; 4.8; 6.4	Minor editorial changes
4.2	Strengthen dosage advice; update subheading from ‘Children’ to ‘Paediatric’
4.4	Additional information on meningioma
6.7	Corrected chemical name; added new chemical structure image

Cyprone_50_pi\Feb21/00