Name of the medicine

The active ingredient of Cyprone tablets is cyproterone acetate.

The chemical name for cyproterone acetate is 6-chloro-17-hydroxy-1α,2α-methylenepregna-4,6-diene-3,20-dione acetate. Its structural formula is:

![Structural formula of cyproterone acetate]

Molecular formula: C_{24}H_{29}ClO_{4}  
Molecular weight: 416.94  
CAS Registry No.: 427-51-0

Description

Cyproterone acetate is a white to pale yellow, odourless crystalline powder. It is practically insoluble in water.

Each Cyprone tablet contains 50 mg of cyproterone acetate.

The tablets also contain the following inactive excipients: lactose, maize starch, povidone, colloidal anhydrous silica and magnesium stearate. *The tablets are gluten free.*

Pharmacology

Cyproterone acetate is a synthetic antiandrogenic hormone preparation. It 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 antigonadotrophic 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 therapy. The function of androgen dependent target organs, such as the prostate, is restricted.

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

Treatment with cyproterone acetate in women diminishes hirsutism and also reduces both androgen dependent loss of scalp hair and elevated sebaceous gland function. The drug also inhibits ovarian function during treatment.
Prolactin levels can increase slightly under higher doses of cyproterone acetate. Studies showed increased prolactin levels up to 20ng/mL (normal range 5-15ng/mL). There are no data for periods longer than 6 months.

Pharmacokinetics

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±12.8h. The total clearance of cyproterone acetate from serum was determined to be 3.5±1.5mL/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 100mg oral and 300mg intramuscular depot administration and was found to be 80 ±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 2mg cyproterone acetate in combination with 35mg ethinyloestradiol, 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 metabolized by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15[β]-hydroxy derivative. Some dose parts are excreted unchanged with bile fluid.

Elimination: In a study in 6 women administered a C14 labelled dose of 2 mg CPA in combination with 50mg 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.

Indications

Women. Moderately severe to severe signs of androgenisation. This includes 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.

Cyproterone acetate inhibits the influence of male sex hormones which are also produced by the female. It is therefore possible to treat diseases in women which are caused by either an 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 is taken during pregnancy, signs of feminisation may occur in the male fetus. Therefore, in women of childbearing potential, pregnancy must be excluded prior to treatment and ethinyloestradiol taken as well to ensure contraception. This also promotes regular menstruation.

Men. Reduction of drive in sexual deviations. Cyproterone acetate 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 therapy 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.** Cyprone is indicated:

- 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.

**Contraindications**

Pregnancy, lactation, liver diseases, a history of or existing hepatic tumours (in carcinoma of the prostate only if these are not due to metastases), a history of jaundice or persistent itching during a previous pregnancy, a history of herpes of pregnancy, Dubin-Johnson syndrome, Rotor syndrome, wasting diseases (with the exception of carcinoma of the prostate), severe chronic depression, previous or existing thromboembolic processes, severe diabetes with vascular changes, sickle-cell anaemia and hypersensitivity to any of the components of Cyprone.

Careful consideration of the risk/benefit ratio must be made in each individual case before Cyprone is prescribed to patients with prostatic carcinoma presenting with a history of thromboembolic processes or suffering from sickle-cell anaemia, or from severe diabetes with vascular changes.

Cyprone 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.

**Precautions**

A thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out in women before the start of therapy. 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. The long-term effects on female fertility are not known with certainty. If, during the combined treatment, persistent or recurrent bleeding occurs at irregular intervals, a gynaecological examination must be carried out to exclude organic diseases.

Patients whose occupation demands great concentration (e.g. road users, machine operators) should be advised that Cyprone can lead to tiredness and diminished vitality, and can impair the ability to concentrate.

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. After discontinuation of therapy, spermatogenesis has taken 3 to 20 months to return to normal.

The sexual drive reduction effect of cyproterone acetate can be diminished under the disinhibitory influence of alcohol.

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

Liver function, adrenocortical function and red blood cell count should be checked regularly during treatment. In diabetics, carbohydrate metabolism should be monitored carefully. The requirement for oral antidiabetics or insulin can change.

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200 to 300 mg cyproterone acetate. Most reported cases are in men with
prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

In rare cases benign, and in even rarer cases malignant liver tumours leading in isolated cases 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. Strict medical supervision is necessary if the patient suffers from diabetes.

A sensation of shortness of breath may occur in individual cases under high-dosed treatment with cyproterone acetate. 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.

In some cases, the occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone acetate. However, a causal relationship seems to be questionable.

In regards to the additional use of a combined oral contraceptive preparation, attention should be drawn to all the data contained in the product information of this product.

Use in Pregnancy (Category: D)

The use of Cyprone is contraindicated during pregnancy (see 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 feminization in male fetuses.

Use in Lactation

The use of Cyprone is contraindicated during lactation, as small amounts of cyproterone acetate are excreted in breast milk (see Contraindications).

Effect on ability to drive or operate machinery

In patients whose occupations demands great concentration (e.g. road users, machine operators), it should be pointed out that Cyprone can lead to tiredness and diminished vitality and can impair the ability to concentrate.

Preclinical findings

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, further tests showed that cyproterone acetate was capable of producing adducts in vivo with DNA in liver cells from rats 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 regimens for cyproterone acetate. One in vivo consequence of cyproterone acetate treatment was the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats.

The clinical relevance of these findings is presently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man.

Carcinogenesis

Cyproterone acetate 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 Androcur. In vivo consequences of CPA treatment were the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats, and an increase of mutation frequency in transgenic rats carrying a bacterial gene as target for mutation. The clinical relevance of these findings presently remains uncertain.

Long-term animal carcinogenicity studies were performed in rats and mice. In one rat study, an increased incidence of hepatomas was reported at oral dose levels of 50mg/kg CPA and above. In mouse (and a second rat) carcinogenicity studies, increases in benign proliferative changes (nodular hyperplasia) in liver cells of female mice and male and female rats were reported at oral doses of 2mg/kg. Because of shortcomings in these studies (inadequate pharmacokinetic data and the need to reassess the 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.

**Impairment on Fertility**

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. After discontinuation of therapy, spermatogenesis has taken 3 to 20 months to return to normal.

**Interactions**

The requirement for oral antidiabetics or insulin can change.

**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.

Common greater than or equal to 1/100 and <1/10; uncommon greater than or equal to 1/1,000 and <1/100; rare greater than or equal to 1/10,000 and <1/1,000; very rare <1/10,000.

**General:**
Very common: tiredness, weight increase
Common: headache, depressive moods

**Cardiovascular:**
Common: thrombotic phenomena

**Gastrointestinal:**
Common: nausea and other gastrointestinal complaints

**Reproductive:**
Very common: Diminished libido
Common: mastodynia, irregular menstrual cycles

**Skin**
Rare: rash
Over the course of several weeks, Cyprone gradually impairs spermatogenesis as a result of the antiandrogenic and antigonadotropic actions. Spermatogenesis recovers gradually within several months of discontinuing therapy.

In male patients Cyprone occasionally leads to gynaecomastia (sometimes combined with tenderness to touch of the breast) which usually regresses after withdrawal of the preparation or reduction of the dose.

As with other antiandrogenic treatments, in male patients long-term androgen deprivation with Cyprone 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 Cyprone 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 reactions have been reported at the approximate frequencies (not necessarily implicating a causal relationship) indicated below.

Common greater than or equal to 1/100 and <1/10; uncommon greater than or equal to 1/1,000 and <1/100; rare greater than or equal to 1/10,000 and <1/1,000; very rare <1/10,000.

General:
Very rare: tiredness, weight increase, headache, depressive moods, sleep disturbances, hot flushes, allergic reactions.

Cardiovascular:
Very rare: thrombotic phenomena, tachycardia

Gastrointestinal:
Very rare: nausea and other gastrointestinal complaints

Hepatobiliary:
Rare: increased liver enzymes, jaundice
Very rare: hepatitis, liver function disturbance, hepatic failure

Reproductive:
Very rare: Diminished libido, irregular menstrual cycles, impaired spermatogenesis, inhibition of ovulation, gynaecomastia, breast tenderness, breast pain, galactorrhea, increased libido

Skin:
Very rare: rash

Dosage and Administration

Women. Cyprone must not be taken by pregnant women. Pregnancy must be excluded before therapy is commenced in women of childbearing potential.

In women of childbearing potential, treatment is commenced on the first 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 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 Cyprone 50 mg tablet taken daily for 10 days per month (from the first to the tenth 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 androgenisation, two Cyprone 50 mg tablets are to be taken daily from the first to the tenth day of the cycle (i.e. 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 one 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. If bleeding fails to occur after this cycle, pregnancy must be excluded before tablet-taking is resumed.

Missed Cyprone tablets may diminish the therapeutic efficacy and may lead to intermenstrual bleeding. The missed Cyprone 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 7 day tablet free interval is observed after 21 days, during which time withdrawal bleeding occurs. 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 interval, the possibility of pregnancy must be excluded before restarting tablet taking. Following clinical improvement, the daily dose of Cyprone may be reduced to 1 or 1/2 a 50 mg tablet during the 10 days on which it is given in each treatment cycle. The dose regimen for combined oral contraceptive preparation remains unchanged. If improvement is maintained over a further few months, cyproterone acetate 10 mg daily from the first to the fifteenth day of the cycle (i.e. 15 days) may be sufficient.

Contraceptive efficacy may be impaired as the dose of Cyprone is reduced. Therefore, a reliable form of contraception (not the rhythm or temperature methods) must be employed during treatment. If a nonhormonal method is adopted, ethinyloestradiol from day 5 to 25 will need to be continued to stabilise the cycle.

Post-menopausal and hysterectomised women. Cyprone may be administered alone in postmenopausal or hysterectomised patients. According to the severity of the complaints, the average dose should be 1/2 to 1 Cyprone 50 mg tablet 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. When treatment is stopped, hirsutism and alopecia are likely to recur.

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 and further increased by cigarette smoking, hypertension, obesity, diabetes, hypercholesterolaemia, or a history of pre-eclamptic toxaemia. This risk of myocardial infarction is substantially increased in women aged 40 and over. All users of combined oestrogen-progestogen medications should be encouraged not to smoke.

Therapy should be discontinued if practical at least 6 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.

A rise in blood pressure may be experienced by susceptible women. 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 mammograms, 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 combined oestrogen-progestogen treatment users of 2 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 is desirable, with particular reference to blood pressure, breasts, abdomen and pelvic organs. A Papanicolaou smear and urinalysis should be carried out.

Some degree of fluid retention may be caused by combined oestrogen-progestogen treatment. 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.

Combined oestrogen-progestogen treatment may cause a reduction in pyridoxine and folate plasma levels. 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:

(a) **Liver functions**: transaminases (AST, ALT) and bromsulfophthalein retention are increased.

(b) **Clotting factors**: VII, VIII, IX and X, prothrombin, platelet aggregation are increased, but antithrombin III decreased.

(c) **Thyroid functions**: thyroid binding globulin (TBG), total thyroxin (T₄) and protein bound iodine (PBI) are increased. T₃ resin uptake (reflecting TBG) is decreased, whilst free T₄ and clinical thyroid state remain unaltered.

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

(e) **Agglutination reactions**: false positive rheumatoid factor and antinuclear factor are increased.

(f) Blood glucose, phospholipids and triglycerides are increased. These tests usually return to pretherapy values shortly after discontinuation of oestrogen-progestogen treatment.
Men. Reduction of drive in sexual deviation. The individual dose will be determined by the response. Generally, treatment is started with one Cyprone 50 mg tablet twice daily. It may be necessary to increase the dose to two Cyprone 50 mg tablets twice daily, or even two Cyprone 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 Cyprone 50 mg tablet twice daily is sufficient. When establishing the maintenance dose or when discontinuing treatment, the dosage should be reduced gradually. Therefore, the daily dose should be reduced by 1 tablet, or better, 1/2 tablet, at intervals of several weeks. To stabilise the therapeutic effect, it is necessary to take Cyprone 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 100mg (2 tablets Cyprone 50mg) twice daily alone for 5 - 7 days, then 100mg (2 tablets Cyprone 50mg) twice daily for 3 - 4 weeks together with an LH-RH agonist in the dosage recommended by the manufacturer.

In long term palliative treatment of advanced prostate cancer in patients who have not had an orchiectomy: 100mg (2 tablets Cyprone 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 LH-RH analogues or who have had orchiectomy: 50mg once to three times daily with upward titration to 100mg three times daily if necessary.

The tablets are to be taken with some liquid after meals. Treatment should not be interrupted, nor the dosage reduced after improvement or remissions have occurred.

Overdosage

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

In cases of overdosage, it is advisable to contact the Poisons Information Centre (131126) for recommendation on the management and treatment of overdosage.

Presentation and Storage Conditions

Cyprone Cyproterone acetate 50 mg tablet: white, marked CY/50 on one side, G on the reverse; 20's, 50's.

Store below 30°C. The tablets should be dispensed and stored in the original container. The tablets should be protected from light.

Name and Address of the Sponsor

Alphapharm Pty Limited
Chase Building 2
Wentworth Park Road
Glebe NSW 2037

ABN 93 002 359 739

www.alphapharm.com.au
Poison Schedule of Medicine

S4 – Prescription Only Medicine

Date of Approval

Approved by the Therapeutic Goods Administration on 31 January 1996.
Date of most recent amendment: 04 December 2006.