Product Information

Anterone 50

Name of the Medicine
Cyproterone acetate. The chemical name is 6-chloro-17-hydroxy-1α, 2α-methylene-pregna-4,6-diene-3,20-dione acetate.

Structural formula:

![Structural formula image]

Molecular formula:
C₂₄H₂₉ClO₄

Molecular weight:
416.95

CAS Number
427-51-0

Description
White circular flat bevelled tablets, with breakline on one side and plain on the other. Anterone 50 contains the active ingredient cyproterone acetate 50mg and the following excipients: lactose, starch (maize), povidone, magnesium stearate, colloidal silicon dioxide and pregelatinised starch (maize).

Pharmacology
Following oral administration, cyproterone acetate is absorbed slowly. Its bio-availability is unknown. The maximum plasma level is reached 3 to 4 hours after ingestion.

Cyproterone acetate is eliminated with a half-life of 38 ± 5 h. After 10 days, 33 ± 6% of the dose can be demonstrated in the urine and 60 ± 8% in the faeces. Cyproterone acetate is eliminated with the urine mainly in the form of unconjugated metabolites and with the bile in the form of glucuronidized metabolites, the main one being 15β-hydroxy-cyproterone acetate.

Radioimmunoassays show that about 0.2% of the dose is eliminated with the breast milk.
Cyproterone 50mg is an antiandrogenic hormone preparation. Cyproterone acetate is believed to prevent the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. The stimulating effect of male sex hormones on androgen-dependent structures and functions is weakened or counteracted by cyproterone acetate.

Cyproterone acetate also exerts a progestational and antigonadotropic effect. Treatment with cyproterone acetate in men results in a reduction of sexual drive and potency and inhibition of gonadal function. These changes are reversible following discontinuation of the therapy. The function of androgen-dependent target organs, such as the prostate, is restricted.

Prostatic carcinoma and its metastases are in general androgen-dependent. Cyproterone 50mg exerts a direct antiandrogenic action on the tumour and its metastases and in addition it exerts a negative feedback effect on the hypothalamic receptors, so leading to a reduction in gonadotropin release, and hence to diminished production of testicular androgens.

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

**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 cyproterone is taken during pregnancy, the properties of the preparation may lead to signs of feminisation in the male foetus. Therefore, in women of child bearing potential, pregnancy must be excluded at the commencement of treatment and ethinyl oestradiol taken as well to ensure contraception. This also promotes regular menstruation.

**MEN**
- Reduction of drive in sexual deviations

Cyproterone 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.

Cyproterone 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.

**Contraindications**

Pregnancy, lactation, liver diseases, a history of 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 herpetic 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. Hypersensitivity to the active substance or to any of the excipients.

In patients with prostatic carcinoma presenting with a history of thromboembolic processes or suffering from sickle-cell anaemia or from severe diabetes with vascular changes, the risk: benefit ratio must be considered carefully in each individual case before cyproterone is prescribed.

Cyproterone 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**

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 in women. 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 in women of childbearing potential. The long-term effects on female fertility are not known with certainty.

If, during the combined treatment, slight "unscheduled" bleeding occurs during the 3 weeks per cycle in which the tablets are being taken, tablet taking should not be interrupted. However, if the bleeding is heavy, the patient should consult her doctor.

It should be pointed out to patients whose occupation demands great concentration (e.g. road users, machine operators) that cyproterone 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. Spermatogenesis has taken 3 - 20 months to return to normal after discontinuing therapy.

The sexual drive reducing effect can be diminished under the disinhibitory influence of alcohol.

During treatment liver function, adrenocortical function and red-blood cell count should be checked regularly. 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 have been fatal in some cases, has been reported in patients treated with 200-300 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 when ever 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 eg. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

In rare cases benign and even in 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.

A sensation of shortness of breath may occur in individual cases under high-dose treatment with cyproterone. 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 extremely rare cases, the occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone. However, a casual relationship seems to be questionable.

THE FOLLOWING ADDITIONAL INFORMATION IS APPLICABLE TO USE OF ALL CYCLIC COMBINED OESTROGEN/PROGESTERONE THERAPIES, INCLUDING ORAL CONTRACEPTIVES: Use of combined oestrogen/progesterone 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/progestosterone medications should be encouraged not to smoke.

Therapy should be discontinued if feasible 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 protosis, diplopia or migraine. If examination reveals papilloedema or retinal vascular lesions medication should be withdrawn.

Susceptible women may experience a rise in blood pressure. The prevalence of hypertension increases with the duration of use and the age of the patient. Blood pressure should be measured and care should be exercised in prescribing these preparations for patients with hypertension. Regular monitoring of blood pressure is desirable.

The first spontaneous ovulation after stopping combined oestrogen/progestogen treatment is sometimes delayed; and there is evidence of temporary impairment of fertility in some women who discontinue combined oestrogen/progestogen treatment, which appears to be independent of the duration of use. Impairment diminishes with time, but may be evident for 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 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 two or more years. The onset or exacerbation of
migraine or other persistent severe headache requires full discontinuation of combined oestrogen/progestogen treatment pending full investigation.

Contraceptive efficacy may be impaired by drug interactions especially rifampicin, semisynthetic penicillin's and anti-convulsant 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.

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

**Carcinogenicity and Mutagenicity**

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate (CPA). However further tests showed that CPA 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 regimes for CPA. One in vivo consequence of CPA treatment was the increased incidence of focal, possibly preneoplastic, 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.

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 50mg/kg CPA 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 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.

**Use in Pregnancy - Category D**

The use of cyproterone is contraindicated during pregnancy as the properties of the pregnancy may lead to signs of feminisation in the male foetus.

**Use During Lactation**

The use of cyproterone is contraindicated during lactation as small amounts of cyproterone acetate are excreted in breast milk.

**Effects on Laboratory Tests**

Certain changes maybe induced in laboratory data:

a) liver functions; transaminases (SGOT, SGPT) and bromsultophalein retention are increased.

b) clotting factors; VII, VIII, IX and X, prothrombin, platelet aggregation are in increased. But antithrombin 3 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 anti-nuclear factor are increased.
f) blood glucose, phospholipids and triglycerides are increased.

These tests usually return to pre-therapy values shortly after discontinuation of oestrogen/progestogen treatment.

**Adverse reactions**

Over the course of several weeks, cyproterone gradually impairs spermatogenesis. In male patients, cyproterone 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.

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

The following adverse reactions have been reported in clinical trials: Diminished libido 16%, tiredness 13.5%, increase in body weight 11%, mastodynia 8%, nausea and other gastrointestinal complaints 7.4%, cycle irregularity 4%, headache 3.3%, depressive moods 3%, thrombotic phenomena 1.2%.

Other adverse reactions reported at low incidence are: galactorrhoea, sleep disturbances, hot flushes, tachycardia, dysmenorrhoea, vaginal discharge, skin discolouration, striae, allergic reactions, increased libido.

**Dosage and administration**

**WOMEN**

Pregnant women must not take cyproterone. Therefore, pregnancy must be excluded at the time therapy is commenced in women of child bearing potential.

**USE OF ALL CYCLIC COMBINED OESTROGEN/PROGESTERONE THERAPIES. INCLUDING ORAL CONTRACEPTIVES:**

**See Precautions.**

**Women of Child bearing Potential**

In women of child bearing potential, the treatment is commenced on the 5th day of the cycle (1st day of bleeding = 1st 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 5th day of the cycle and the following recommendations then observed.

For hirsutism secondary to female androgenization, the usual starting dose should be one tablet of Anterone 50 taken daily for 10 days per month (from the 5th to the 14th day of the cycle). Once a satisfactory response has been attained it is usually possible to reduce the dose further. Doses as low as 10mg 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, two tablets of Anterone 50 are to be taken daily with some liquid after a meal from the 5th to the 14th day of the cycle (= for 10 days). In addition, these women should receive ethinyl oestradiol 50 micrograms daily from the 5th to the 25th day of the cycle to provide the necessary contraceptive protection and to stabilise the cycle.

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. The use of Anterone 50 and ethinyl oestradiol should nevertheless be continued according to instructions, ignoring the missed tablet or tablets, in order to avoid premature bleeding in this cycle. However, an additional non-hormonal barrier method of contraception (not the rhythm or temperature methods) is to be employed for the rest of the cycle.

A 7-day tablet-free interval is observed after 21 days, during which time a 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 Anterone 50 may be reduced to 1 or ½ tablet during the 10 days on which it is given in each cycle. The dose regimen for ethinyl oestradiol remains unchanged. If improvement is maintained over a further few months, Anterone 50 daily from the 5th to the 19th day of the cycle (= 15 days), may be sufficient.

As the dose of Anterone 50 is reduced, contraceptive efficacy may be impaired.

Therefore a reliable form of contraception (not the rhythm or temperature methods) must be employed during treatment. If a non-hormonal method is adopted, ethinyl oestradiol from day 5 to 25 will need to be continued to stabilise the cycle.

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

Postmenopausal or Hysterectomised Women
In postmenopausal or hysterectomised patients Anterone 50 may be administered alone. According to the severity of the complaints, the average dose should be ½ to one tablet Anterone 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 androgenization and response to treatment. Treatment is usually carried out over several months initially. Acne and seborrhoea usually respond sooner than hirsutism or alopecia. Hirsutism and alopecia are likely to recur when treatment is stopped.

MEN
• reduction in the drive of sexual deviation
The individual dose will be determined by the response. Generally, treatment is started with one 50mg tablet twice daily. It may be necessary to increase the dose to two 50mg tablets twice daily, or even two 50mg 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 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 Anterone 50 over a protracted period of time, if possible with the simultaneous use of psychotherapeutic measures.

The tablets are to be taken with some liquid after meals.
- Inoperable prostatic carcinoma
  - to suppress LHRH analogue "flare" - 300mg/day which may be reduced to 200mg/day
  - in long-term palliative treatment - After orchidectomy, two 50mg tablets once to twice daily. Without orchidectomy, two 50 mg tablets 2 to 3 times daily.
  - In the treatment of hot flushes - low initial dose with upward titration 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.

**Presentation and Storage Condition**
Anterone 50: White circular flat bevelled tablets, with breakline on one side and plain on the other.

Anterone 50 tablets presented in pvc/pvdc/aluminium foil blisters. Each pack contains 20 or 50 tablets

**Storage**
Store below 25°C.

**Name and Address of the Sponsor**
Cipla Australia Pty Ltd
Level 1, 132-136 Albert Road
South Melbourne VIC 3205

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