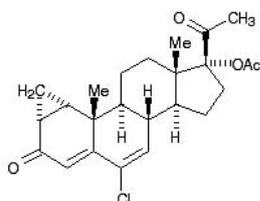


PRODUCT INFORMATION CYPROTERONE SANDOZ® 50 MG TABLETS

NAME OF THE MEDICINE

Cyproterone acetate

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



CAS [427-51-0]

Empirical formula: C₂₄H₂₉ClO₄ MW: 416.94

DESCRIPTION

Active: cyproterone acetate.

Excipients: lactose, microcrystalline cellulose,, croscarmellose sodium, povidone and magnesium stearate.

Cyproterone Sandoz 50 mg AUST R 107330

Cyproterone acetate is a white to pale yellow crystalline powder. Melting point: 206 to 213°C. 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.

PHARMACOLOGY

Pharmacodynamics

Cyproterone acetate is believed to prevent the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. The stimulating effect of male sex hormones on androgen dependent structures and functions is weakened or counteracted by cyproterone acetate.

Cyproterone acetate also exerts a progestational and anti-gonadotrophic effect.

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

Prostatic carcinoma and its metastases are in general androgen dependent. Cyproterone acetate exerts a direct 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.

Serum prolactin levels may increase with higher doses of CPA. Prolactin levels increased up to 20ng/mL (normal range 5-15ng/mL) in studies of up to six months duration. There are no data for periods longer than six months.

Pharmacokinetics

Absorption. Following oral administration, cyproterone acetate is absorbed slowly. Relative bioavailability was calculated from a dose-corrected comparison of area under the curves of serum levels after 100mg oral and 300mg intramuscular depot administration in 8 young women, and was found to be $80 \pm 30\%$ (range 23% - 199%). In a study to determine the bioequivalence of the Cyproterone Sandoz 100mg formulation in comparison to 100mg cyproterone acetate tablets distributed by Schering Proprietary Ltd, the mean peak plasma concentration for cyproterone acetate from the Cyproterone Sandoz 100 formulation after administration of a single 100mg dose, was 176.2ng/mL at about 4 hours in comparison to 161.7ng/mL after about 3 hours for the reference product. The 90% Confidence Interval (CI) for comparison of the log transformed peak concentrations was 0.97 – 1.22. The Area Under the Plasma Concentration-Time curve ($AUC_{0-\infty}$) was 5756.0ng.h/mL for the Cyproterone Sandoz 100mg formulation versus 5953.3ng.h/mL for 100mg cyproterone acetate tablets distributed by Schering Proprietary Ltd with the 90% Confidence Interval (CI) for comparison of the log transformed data being 0.91 – 1.03.

Distribution. Cyproterone acetate within the cardiovascular system is almost exclusively bound to plasma albumin. About 3.5 - 4% of total drug levels are present unbound. Because protein binding is non-specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate. In animals, cyproterone acetate has been shown to distribute into the liver, kidney, brain and heart. Levels in these organs may be higher than in plasma.

Metabolism. Cyproterone acetate is metabolised by various pathways, including hydroxylations and glucuronide conjugations. The main metabolite in human plasma is 15 β -hydroxycyproterone acetate.

Elimination. Some drug is excreted unchanged with bile fluid. Most of the dose is excreted in the form of metabolites at a urinary to biliary ratio of 3:7. Unconjugated metabolites appear in the urine whereas glucuronide metabolites appear in the bile. In the study discussed above, cyproterone acetate was eliminated with a mean half-life of approximately 70 hours for both preparations.

Steady state conditions. An accumulation of cyproterone acetate in the serum by a factor of about 3 can be expected during repeated daily administration.

Radioimmunoassays show that about 0.2% of the dose is eliminated with the breast milk.

INDICATIONS

Women

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

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

Men

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

Inoperable prostatic carcinoma. To suppress flare with initial luteinising hormone releasing hormone (LHRH) analogue therapy; in long-term palliative treatment where LHRH analogues or surgery are ineffective, not tolerated, contraindicated or where oral therapy is

preferred; in the treatment of hot flushes in patients treated with LHRH analogues or who have had orchidectomy.

CONTRAINDICATIONS

Pregnancy, lactation, hepatic 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, presence or history of meningioma.

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 Sandoz 50mg.

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 Sandoz 50mg is prescribed.

Cyproterone Sandoz 50mg 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.

Hypersensitivity to any of the components of Cyproterone Sandoz 50mg.

PRECAUTIONS

During treatment, hepatic function, adrenocortical function and red blood cell count should be checked regularly. In patients with diabetes, strict medical supervision is necessary. Carbohydrate metabolism should be monitored carefully.

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.

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with cyproterone acetate 200 to 300mg daily. Most reported cases are in men with prostatic cancer. Toxicity is dose related and usually develops several months after treatment has begun. Liver function tests should be performed pretreatment 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, eg. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk. Benign and malignant hepatic tumours, leading very rarely to life-threatening intra-abdominal haemorrhage, have been observed in isolated cases after the use of hormonal steroids. If severe upper abdominal complaints, hepatic enlargement or signs of intra-abdominal haemorrhage occur, a hepatic tumour should be included in the differential diagnostic considerations and, if necessary, discontinuation of the preparation considered.

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

A sensation of shortness of breath may occur in individual cases under high dose treatment with Cyproterone Sandoz 50mg. 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.

The occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone acetate. However, 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.

During treatment adrenocortical function should be checked regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of Cyproterone Sandoz with high doses.

Anaemia has been reported during treatment with Cyproterone Sandoz. Therefore, the red-blood cell count should be checked regularly during treatment.

Other conditions

Cyproterone Sandoz tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose mal-absorption should not take this medicine.

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

Specifically to be observed in men. The sexual drive reduction effect of Cyproterone Sandoz 50mg can be diminished under the disinhibitory influence of alcohol.

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 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 treatment in women of childbearing potential.

If persistent mid-cycle bleeding, irregular or heavy bleeding occurs, a gynaecological examination must be carried out to exclude organic disease.

Combined Cyproterone acetate/oestrogen-progestogen therapy. See also DOSAGE AND ADMINISTRATION, Women of childbearing potential.

With the additional use of a combined oral contraceptive preparation, refer to the Product Information for that product.

The following additional information is applicable to use of all cyclic combined oestrogen-progestogen therapies, including oral contraceptives.

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

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

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

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

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

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

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

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

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

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

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

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

Thyroid function tests: Thyroid binding globulin (TBG), Total thyroxine (T₄), and protein bound iodine (PBI) are increased. T₃ resin uptake (reflecting TBG) is decreased, whilst free T₄ and clinical thyroid state remain unaltered.

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

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

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

Effects on fertility

Spermatogenesis is impaired during treatment and recovers gradually after discontinuation. See ADVERSE 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 to 20 months to return to normal after discontinuing therapy.

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

Use in pregnancy (Category D)

The use of Cyproterone Sandoz 50mg is contraindicated during pregnancy (see CONTRAINDICATIONS). Administration of cyproterone acetate during the hormone sensitive differentiation phase of the genital organs (after approximately 45 days of pregnancy) could lead to signs of feminisation in the male fetus.

Australian Pregnancy Categorisation – Category D. Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Use in lactation

The use of Cyproterone Sandoz 50mg is contraindicated during lactation, as small amounts of cyproterone acetate are excreted in breast milk (see CONTRAINDICATIONS).

Use in elderly

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

Carcinogenicity and Genotoxicity

Cyproterone acetate (CPA) was negative in a standard battery of genotoxicity studies. However, further tests showed that CPA was capable of producing hepatocyte DNA adducts in rats, dogs and monkeys (and an increase in DNA-repair activity in rats) in vivo, and also in freshly isolated rat and human liver cells in vitro. This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for Cyproterone Sandoz 50mg. 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 liver pathology), the carcinogenic potential of CPA in animals could not be determined.

Clinical experience and limited epidemiological data available to date do not appear to have supported an increased incidence of hepatic tumours in humans. However it must be borne in mind that steroidal sex hormones can promote the growth of certain hormone-dependent tissues and tumours.

Effect on ability to drive or operate machinery

It should be pointed out to patients whose occupation demands great concentration (eg. road users, machine operators) that Cyproterone Sandoz 50mg can lead to tiredness and diminished vitality and can impair the ability to concentrate.

INTERACTIONS WITH OTHER MEDICINES

The requirement for oral antidiabetics or insulin may 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 levels of cyproterone acetate.

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

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

ADVERSE EFFECTS

Adverse reactions reported in clinical trials

The following adverse reactions have been reported at the approximate frequencies (not necessarily implicating a causal relationship) indicated below.

Very common greater than or equal to 1/10; 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.

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

The most frequently observed ADRs in male patients receiving Cyproterone Sandoz are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious ADRs in patients receiving Cyproterone Sandoz are hepatic toxicity, benign and malignant liver tumour.

Over the course of several weeks, Cyproterone Sandoz 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 Sandoz 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 Cyproterone Sandoz 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 dose Cyproterone Sandoz treatment.

Changes in bodyweight are possible.

Other adverse events reported at a low incidence were dysmenorrhoea, vaginal discharge, skin discolouration, striae.

Postmarketing information

The following adverse reactions have been reported at the approximate frequencies (not necessarily implicating a causal relationship) indicated below.

Very common greater than or equal to 1/10; 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

Common. Fatigue, hot flushes, sweating.

Very rare. Tiredness, headache, sleep disturbances.

Cardiovascular

Very rare. Thrombotic phenomena, tachycardia.

Gastrointestinal

Very rare. Nausea and other gastrointestinal complaints.

Hepatobiliary

Common. Hepatic toxicity, including jaundice, hepatitis, hepatic failure

Rare. Increased liver enzymes, jaundice.

Very rare. Hepatitis, liver function disturbance, hepatic failure.

Reproductive system and breast disorders

Very common. Reversible inhibition of spermatogenesis, inhibition of ovulation.

Common. Gynaecomastia (men), breast tenderness (women).

Very rare. Irregular menstrual cycles, impaired spermatogenesis, breast pain, galactorrhea.

Skin

Uncommon. Rash.

Musculoskeletal and connective tissue disorders

Very rare. Osteoporosis (men).

Immune system disorders

Rare: Hypersensitivity reaction.

Metabolic and nutrition disorders

Common: Weight increased or weight decreased.

Psychiatric disorders

Very common. Libido decreased (men), erectile dysfunction.

Common. Depressed mood, restlessness (temporary).

Uncommon. Libido decreased (women).

Rare. Libido increased (women).

Neoplasms benign and malignant

Very rare. Benign & malignant liver tumours

Respiratory, thoracic and mediastinal disorders

Common. Shortness of breath

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 Sandoz, 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 Cyproterone Sandoz doses of 25mg and above (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

The tablets are to be taken with some liquid after meals.

Women

Women of child-bearing potential

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

Hirsutism secondary to female androgenisation

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

Other severe signs of androgenisation

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

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

Combined cyproterone acetate/oestrogen-progestogen therapy

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

Women receiving the cyclical combined therapy should take their tablets at the same time each day. If a tablet is missed and if more than 12 hours elapse from this time ie. more than 36 hours have elapsed since the last tablets were taken), contraceptive protection in this cycle may be reduced. The use of Cyproterone Sandoz 50mg and a combined oral contraceptive containing low dose oestrogen should nevertheless be continued according to

the instructions, ignoring the missed tablet or tablets, in order to avoid premature bleeding in this cycle. However, an additional nonhormonal barrier method of contraception (not the rhythm or temperature methods) is to be employed for the rest of the cycle.

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

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

As the dose of cyproterone acetate is reduced, contraceptive efficacy may be impaired. Therefore, a reliable form of contraception (not the rhythm or temperature methods) must be employed during treatment. If a nonhormonal method is adopted, a combined oral contraceptive containing low dose oestrogen from day five to 25 will need to be continued to stabilise the cycle.

See also PRECAUTIONS, Combined cyproterone acetate/oestrogen-progestogen therapy.

Postmenopausal and hysterectomised women

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

Duration of treatment

The duration of treatment depends on the severity of the pathological signs of androgenisation and response to treatment. Treatment is usually carried out over several months initially. Acne and seborrhoea usually respond sooner than hirsutism or alopecia. Hirsutism and alopecia are likely to recur when treatment is stopped.

Men

Reduction of drive in sexual deviation

The individual dose will be determined by the response. Generally, treatment is started with one 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 half a tablet twice daily is sufficient. When establishing the maintenance dose or when discontinuing the preparation, the dosage should not be reduced abruptly, but gradually. To this end, the daily dose should be reduced by one tablet, or better, by half a tablet, at intervals of several weeks.

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

Inoperable prostatic carcinoma

Suppression of "flare" with initial LHRH analogue therapy. Initially 100mg twice daily alone for 5-7 days, then 100mg twice daily for 3-4 weeks together with an LHRH agonist at the dosage recommended by the manufacturer.

Long-term palliative treatment without orchidectomy. 100mg two or three times daily. Treatment should not be interrupted, nor the dosage reduced, after improvement or remissions have occurred.

Treatment of hot flushes (in patients treated with LHRH analogues or post-orchidectomy). Low initial dose of 50mg once to three times daily, with upward titration to 100mg three times daily if necessary.

See PRECAUTIONS, ADVERSE EFFECTS and OVERDOSAGE.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

There is no experience in overdose and individual clinical assessment and symptomatic treatment is required immediately as appropriate.

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

PRESENTATION AND STORAGE CONDITIONS

Cyproterone Sandoz 50 mg Tablets - white, round, flat tablet marked 50 with a scoreline on one face, plain on the other.

Cyproterone Sandoz 50mg is available in bottles of 20 and 50 tablets.

Store below 30 °C.

Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 15
November 2004

Date of most recent amendment: 18/02/2016