

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg cyproterone acetate.

Excipient with known effect : lactose 208.894mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White oblong tablets, with a break bar on both sides, embossed "C1" on one side..

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of patients with prostatic cancer (1) to suppress "flare" with initial LHRH analogue therapy,(2) in long-term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or where oral therapy is preferred, and (3) in the treatment of hot flushes in patients under treatment with LHRH analogues or who have had orchidectomy.

4.2 Posology and method of administration

Posology :

Adults

The maximum daily

dose is 300 mg.

For long-term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or where oral therapy is preferred the dosage is 200-300 mg/day.

Dosage for suppression of "flare" with initial LHRH analogue therapy:

Initially 1 tablet of Cyproterone Acetate 100 mg twice daily (200 mg) alone for 5 - 7 days, followed by 1 tablet of Cyproterone Acetate 100 mg twice daily (200 mg) for 3 – 4 weeks together with the LHRH analogue therapy in the dosage recommended by the marketing authorisation holder (see SmPC of LHRH analogue).

For the above two indications the dosage should be divided into 2 - 3 doses per day and taken with some liquid after meals.

For the treatment of hot flushes in patients under treatment with LHRH analogues or who have had orchidectomy a 50 mg starting dose, with upward titration if necessary within the range 50-150 mg/day, is recommended. For this indication the dosage should be divided into 1 - 3 doses per day and taken with some liquid after meals.

Additional information on special populations

Paediatric population: Cyproterone Acetate is not recommended for use in male children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Cyproterone Acetate must not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and the still unestablished axes of endocrine function cannot be ruled out.

Elderly:

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

Patients with hepatic impairment:

The use of Cyproterone Acetate is contraindicated in patients with liver diseases (see section 4.4 and 4.8).

Renal impairment:

The use of Cyproterone Acetate in patients with renal impairment has not been investigated. There are no data suggesting the need for dosage adjustment in patients with renal impairment (see section 5.2).

Method of administration

For oral administration.

4.3 Contraindications

Cyproterone Acetate must not be used in patients with:

- Meningioma or a history of meningioma.
- Liver diseases (including Dubin-Johnson syndrome and Rotor syndrome)
- Malignant tumours (except for carcinoma of the prostate)
- Previous or existing liver tumours (only if these are not due to metastases from carcinoma of the prostate)
- Wasting diseases (with the exception of inoperable carcinoma of the prostate)
- Existing thromboembolic processes
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 also been reported. Most reported fatal cases were in men with advanced prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment, regularly during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should be withdrawn, unless the 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 very rare cases benign and malignant liver tumours, which may lead to life-threatening intra-abdominal haemorrhage, have been observed after the use of Cyproterone Acetate. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis.

Thromboembolic events: The occurrence of thromboembolic events has been reported in patients using Cyproterone Acetate, although a causal relationship has not been established. Patients with previous arterial or venous thrombotic / thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infarction), with a history of cerebrovascular accidents or with advanced malignancies are at increased risk of further thromboembolic events, and may be at risk of recurrence of the disease during Cyproterone Acetate therapy.

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

Meningiomas:

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

Chronic depression: It has been found that some patients with severe chronic depression deteriorate whilst taking Cyproterone Acetate therapy. Such patients should be closely monitored for signs of deterioration and warned to contact their doctor immediately if their depression worsens.

Shortness of breath: Shortness of breath may occur under high-dosed treatment with Cyproterone Acetate. This may be due to the stimulatory effect of progesterone and synthetic progestogens on breathing, which is accompanied by hypocapnia and compensatory alkalosis, and which is not considered to require treatment.

Adrenocortical function: During treatment, adrenocortical function should be checked regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of Cyproterone Acetate with high doses (see section 5.3).

Diabetes mellitus: Strict medical supervision is necessary if the patient suffers

from diabetes as Cyproterone Acetate

can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment because the requirement for oral antidiabetics or insulin can change. See also section 4.5.

Anaemia: Anaemia has been reported during long-term treatment. Therefore, the red blood cell count should be checked regularly during treatment.

Lactose : Cyproterone Acetate 100mg contains 208.894mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Patients who are on a lactose-free diet should take this amount into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

Diabetes: At high therapeutic cyproterone acetate doses of three times 100mg per day, cyproterone acetate may inhibit CYP2C8 (see below). Thiazolidinediones (i.e. the anti-diabetics pioglitazone and rosiglitazone) are

substrates of CYP2C8 (increased blood levels of these anti-diabetics may require dose adjustment).

Other interactions: Clinical interaction studies have not been performed. However, since cyproterone acetate is metabolised 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 rifampicin, phenytoin and products containing St. John's wort may reduce the levels of cyproterone acetate.

Based on in vitro inhibition studies, an inhibition of the cytochrome P450 enzymes CYP2C8, 2C9, 2C19, 3A4 and 2D6 is possible at high cyproterone acetate doses of 100 mg three times per day.

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

4.6. Pregnancy and lactation

Not applicable

4.7 Effects on ability to drive and use machines

Fatigue and lassitude are common - patients should be warned about this and if affected should not drive or operate machinery.

4.8 Undesirable effects

The most frequently observed adverse drug reactions (ADRs) in 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.

The following approximate incidences were estimated from published reports of a number of small clinical trials and spontaneous ADR reports:

- very common: incidence \geq 1:10
- common: incidence $<$ 1:10 but \geq 1:100
- uncommon: incidence $<$ 1:100 but \geq 1:1,000

- rare: incidence $< 1:1,000$ but $\geq 1:10,000$
- very rare: incidence $< 1:10,000$
- not known (cannot be estimated from available data)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

- Very rare: Benign and malignant liver tumours which may lead to life-threatening intra-abdominal haemorrhage (see section 4.4).
- Not known: The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25 mg/day and above.

Blood and the lymphatic system disorders

- Not known: Anaemia during long-term treatment (see section 4.4).

Immune system disorders

- Rare: Hypersensitivity reactions.

Endocrine disorders

- Not known: Suppression of adrenocortical function.

Metabolism and nutrition disorders

- Common: Changes in bodyweight during long term treatment (chiefly weight gains in association with fluid retention).

Psychiatric disorders

- Common: Depressive moods and restlessness (temporary).

Vascular disorders

- Not known: Thromboembolic events, although a causal relationship has not been established (see section 4.4).

Respiratory, thoracic and mediastinal disorders

- Common: Dyspnoea (see section 4.4).

Hepato-biliary disorders

- Common: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, has been observed in patients treated with Cyprostat. At dosages of 100 mg and above, cases with fatal outcome have also 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.

Skin and subcutaneous tissue disorders

- Uncommon: Rash.
- Not known: Reduction of sebum production leading to dryness of the skin and improvement of existing acne vulgaris has been reported as well as; transient patchy loss and reduced growth of body hair, increased growth of scalp hair, lightening of hair colour and female type of pubic hair growth.

Musculoskeletal and connective tissue disorders

Not known: Osteoporosis (due to long-term androgen deprivation).

Reproductive system disorders

Very common: Decreased libido, erectile dysfunction, reduced sexual drive and inhibition of gonadal function. These changes are reversible after discontinuation of therapy.

Inhibition of spermatogenesis:

Very common: Sperm count and the volume of ejaculate are reduced.

Infertility is usual, and there may be azoospermia after 8 weeks. There is usually slight atrophy of the seminiferous tubules. Follow-up examinations have shown these changes to be reversible, spermatogenesis usually reverting to its previous state about

3-5 months after stopping Cyproterone Acetate, or in some users, up to 20 months. That spermatogenesis can recover even after very long treatment is not yet known. There is evidence that abnormal sperms which might give rise to malformed embryos are produced during treatment with Cyproterone Acetate.

Gynaecomastia:

Common: Gynaecomastia (sometimes combined with tenderness to touch of the mamillae) which usually regresses after withdrawal of the preparation.

Rare: Galactorrhoea and tender benign nodules.

Symptoms mostly subside after discontinuation of treatment or reduction of dosage.

General disorders and administration site conditions

Common: Hot flushes, sweating, fatigue and lassitude.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There have been no reports of ill-effects of overdosage, which it is, therefore, generally unnecessary to treat. There are no specific antidotes and if treatment is required it should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, antiandrogens, plain, ATC code: G03HA01

Prostatic carcinoma and its metastases are in general androgen-dependent. Cyproterone acetate exerts a direct anti-androgen action on the tumour and its metastases. It also has progestogenic activity, which exerts a negative feedback effect on the hypothalamic receptors, so leading to a reduction in gonadotrophin release, and hence to diminished production of testicular androgens. Sexual drive and potency are reduced and gonadal function is inhibited.

The antigonadotropic effect of cyproterone acetate is also exerted when administered with LHRH analogues. The initial increase of testosterone caused by this class of substances is reduced by cyproterone acetate.

An occasional tendency for the prolactin levels to increase slightly has been observed under higher doses of cyproterone acetate.

5.2 Pharmacokinetic properties

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range. The ingestion of 100 mg of cyproterone acetate gives maximum serum levels of about 239 ng/ml at about 3 hours. Thereafter, drug serum levels declined during a time interval of typically 24 to 120 h, with a terminal half-life of 42.8 ± 9.7 h. The total clearance of cyproterone acetate from serum is 3.8 ± 2.2 ml/min/kg. Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15β -hydroxy derivative.

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. The renal and biliary excretion proceeds with a half-life of 1.9 days. Metabolites from plasma are eliminated at a similar rate (half-life of 1.7 days).

Cyproterone acetate 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.

The absolute bioavailability of cyproterone acetate is almost complete (88 %

of
dose).

5.3 Preclinical safety data

Systemic toxicity

Preclinical data reveal no specific risk for humans based on conventional studies of repeated dose toxicity beyond those discussed in other sections of the SPC.

Experimental investigations produced corticoid-like effects on the adrenal glands in rats and dogs following higher dosages, which could indicate similar effects in humans at the highest given dose (300 mg/day).

Genotoxicity and carcinogenicity

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 with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes, the DNA-adduct level in the dog liver cells was extremely low.

This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. *In vivo* consequences of cyproterone acetate treatment were the increased incidence of focal, possibly preneoplastic, 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 is presently uncertain.

In long-term carcinogenicity studies in rats cyproterone acetate increased the incidence of liver tumours including carcinomas at high doses which concomitantly caused liver toxicity and exceeded the maximum human dose. Further investigations into rodents at lower, non-hepatotoxic doses revealed benign liver proliferations similar to effects described for other steroid hormones. However, it must be borne in mind that sex steroids can promote the growth of certain hormone dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Maize starch
Povidone K 25
Magnesium Stearate (E572)

Colloidal anhydrous silica

6.2. Incompatibilities

None known

6.3. Shelf life

36 months

6.4. Special precautions for storage

None

6.5. Nature and contents of container

Packs of blister strips containing 84 tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Stragen UK Limited
Castle Court
41 London Road
Reigate
Surrey
RH2 9RJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 21844/0002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

15/08/2009

10 DATE OF REVISION OF THE TEXT

06/03/2016