SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate 50 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg cyproterone acetate.

Excipient with known effect

lactose 104.447 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

The tablets are white, round, scored on one side and embossed “50” on the reverse side

4.1 Therapeutic indications

For control of libido in severe hypersexuality and/or sexual deviation in the adult male.

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

For oral administration only.

Control of libido in severe hypersexuality and/or sexual deviation.

Adults and the elderly:
The usual dose is started with 1 tablet Cyproterone Acetate 50 mg twice daily.

When a satisfactory result has been achieved, one should try to maintain the therapeutic effect with the lowest possible dose. When establishing the maintenance dose or when discontinuing the preparation, it is recommended to reduce the dose gradually. The daily dose should be divided and taken after the morning and evening meals.

The management of patients with prostatic cancer

The maximum daily dose is 300mg

Adults and the elderly:

To suppress "flare" with initial LHRH Analogue therapy**:** Initially 2 tablets of Cyproterone Acetate 50 mg twice daily (200 mg) alone for 5-7 days, followed by 2 tablets of Cyproterone Acetate 50 mg twice daily (200 mg) for 3-4 weeks together with the LHRH analogue therapy in the dosage recommended by the marketing authorization holder (see SmPC of LHRH analogue)..

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

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

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

Additional information on special population (applies to all indications)

Paediatric population: Cyproterone Acetate is not recommended for use in male children and adolescents below 18 years of age due to 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 still unstabilised 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).

4.3 Contraindications

Cyproterone acetate must not be used in patients with:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Cyproterone acetate must not be used in patients with meningioma or a history of meningioma.

Cyproterone acetate is contraindicated for use in patients with liver diseases (including Dubin-Johnson syndrome and Rotor syndrome)

malignant tumours (except for carcinoma of the prostate);

Previous or existing liver tumours

wasting diseases (because of transient catabolic action);

a history of or existing thrombosis or embolism;

severe diabetes with vascular changes;

sickle-cell anaemia;

severe chronic depression.

Cyproterone acetate should not be given to youths under the age of 18 or to those whose bone maturation and testicular maturation is incomplete.

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. See also section 4.3.

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: the tablets contains 104.447 mg lactose. 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.

Spermatogenesis: A spermatogram should be recorded before starting treatment in patients of procreative age, as a guard against attribution of pre-existing infertility to cyproterone acetate at a later stage. It should be noted that the decline in spermatogenesis is slow, and cyproterone acetate should, therefore, not be regarded as a male contraceptive.

Medico-legal considerations: Doctors are advised to ensure that the fully informed consent of the patient to cyproterone acetate treatment is witnessed and can be verified.

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).

Chronic alcoholism: Alcohol appears to reduce the effect of cyproterone acetate, which is of no value in chronic alcoholics.

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 of100 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 cyproterone acetate doses, since they share the same metabolic pathway.

4.6 Fertility, 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 ≥ 1:10
-common: incidence <1:10 but ≥1:100
-uncommon: incidence <1:100 but ≥1:1000
-rare: incidence<1:1000 but ≥ 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 25mg/day and above

Blood and 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 nutritional 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: Thromoembolic events, although a causal relationship has not been established (see section 4.4).

Respiratory, thoracic & mediastinal disorders

Common: Dyspnoea (see section 4.4).

Hepatobiliary 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 & subcutaneous tissue disorders

Uncommon: Rash

Not known: Reduction of sebum production leading to dryness of the skin and consequently 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 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 to 5 months after stopping treatment 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.

Gynaecomastia:

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

Rare: Galectorrhoea and tender benign nodules.

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

General and administration site disorders

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 from overdosage, which is, therefore, generally unnecessary to treat. There are no special antidotes and treatment 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 two cyproterone acetate 50 mg tablets gives maximum serum levels of about 285 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 43.9 ± 12.8 h. The total clearance of cyproterone acetate from serum is 3.5 ± 1.5 ml/min/kg. Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15ß-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 revealed 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

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 56 or 168 -tablets

6.6 Special precautions for disposal

No special requirement for disposal

7. MARKETING AUTHORISATION HOLDER

Stragen UK Limited

Castle Court

41 London Road

Reigate

Surrey

RH2 9RJ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 21844/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/08/2009

10 DATE OF REVISION OF THE TEXT

15/12/2016