SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate 100 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg cyproterone acetate.

Excipient: Lactose monohydrate.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Uncoated tablet.
White, capsule shaped tablet with a breakline on one side and ‘CPA 100’ marked on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the 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 an orchidectomy.

4.2 Posology and method of administration

For oral administration only.

Adults and the elderly:

The maximum daily dose is 300mg

To suppress "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 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

Children:

Its use is not recommended in children and adolescents (under 18 years).

Additional information on special population (applies to all indications)

Children and adolescents: 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 patients:

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).

Patients with 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 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

Use in patients known to be hypersensitive to cyproterone acetate or to any of the ingredients of Cyproterone Acetate Tablets.

4.4 Special warnings and precautions for use

Liver: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200 – 300 mg/day 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, regularly during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be attributed to another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

As with other sex steroids, benign and malignant liver changes have been reported in isolated cases.

Very rarely liver tumours, leading in isolated cases to life-threatening intra-abdominal haemorrhage, have been observed after the use of sex steroids, to which class cyproterone acetate belongs. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, hepatic tumour should be considered in the differential diagnosis and, if necessary, cyproterone acetate should be withdrawn.

Thromboembolism: The occurrence of thromboembolic events has been reported in patients using cyproterone acetate, although a causal relationship has not been established. Patients with a history of arterial or venous thrombotic/thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infraction), 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 disorders 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.

In very rare cases, the occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone acetate; a causal relationship seems however questionable.

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

Breathlessness: Shortness of breath may occur. Possibly due to the known stimulatory effect of progesterone and synthetic progestogens on breathing, which is accompanied by hypocapnia and compensatory alkalosis, but it is not considered that treatment is required.

Adrenocortical function: During treatment adrenocortical function should be monitored regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of Cyproterone Acetate.

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.

Haemoglobin: Hypochromic anaemia has been found rarely during long term treatment, and blood counts before and at regular intervals during treatment are advisable.

Nitrogen balance: a negative nitrogen balance is usual at the start of treatment, but usually does not persist.

Lactose: The tablets also contain lactose (see 6.1). 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.

Meningiomas: The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate primarily at doses of 25 mg and above. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate (see section 5.1). High cumulative doses can be reached with prolonged use (several years) or shorter duration with high daily doses. Patients should be monitored for meningiomas in accordance with clinical practice. If a patient treated Cyproterone Acetate is diagnosed with meningioma, treatment with Cyproterone Acetate and other cyproterone containing products must be permanently stopped (see section 'Contraindications').
There is some evidence that the meningioma risk may decrease after treatment discontinuation of cyproterone.

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

4.5 Interaction with other medicinal products and other forms of interaction

Diabetes: The requirement for oral antidiabetic treatment or insulin can change. See also section 4.4. At high therapeutic cyproterone acetate doses of three times 100 mg 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).

Cyproterone acetate can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment.

Chronic alcoholism:Alcohol appears to reduce the effect of cyproterone acetate.

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 inhibits the metabolism of cyproterone acetate. On the other hand, inducers of CYP3A4 such as rifampicine, 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. (This is three times the maximum total daily dose).

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. Cyproterone Acetate Tablets are not indicated for use in women.

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 in the first few weeks of therapy but usually become much less marked from the third month.

The marked lassitude and asthenia necessitate special care when driving or operating 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 incidents 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).
Rare: The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate (see section 4.4).

Blood and lymphatic system disorders
Not known: Anaemia during long-term treatment

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, which has been fatal in some cases have been reported in patients treated with 200-300 mg cyproterone acetate (usually at dosages of 100mg and above) (see section 4.4). 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 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, connective tissue and bone 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 is reduced. Infertility is usual, and there may be azoospermia after eight 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 three to five months after stopping treatment or in
some users up to 20 months. That spermatogenesis can recover even after very long treatment is uncertain. 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been no reports of ill effects from overdosage, therefore, generally it is unnecessary to treat. There are no special antidotes and treatment should be symptomatic. If overdosage is discovered within 2 to 3 hours and is so large that treatment seems desirable, gastric lavage can be safely used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03H AO1

Prostatic carcinoma and its metastases are generally dependent on androgens. Cyproterone acetate is a progestational steroid with strong anti-androgen activities, and in addition cyproterone acetate exerts a negative feedback on the hypothalamic receptors; therefore suppressing gonadotrophin release, and hence secretion of testosterone (and other androgens) is reduced.

Meningioma
Based on results from a French epidemiological cohort study, a cumulative dose-dependent association between cyproterone acetate and meningioma has been observed. This study was based on data from the French Health insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg cyproterone tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥3 g) and women who were slightly exposed to cyproterone acetate (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

Cumulative dose of cyproterone acetate	Incidence rate (in patient-years)	HR_{adj} (95% CI) [a]
Slightly exposed (<3 g)	4.5/100,000	Ref.
Exposed to ≥3 g	23.8/100,000	6.6 [4.0-11.1]
12 to 36 g	26/100,000	6.4 [3.6-11.5]
36 to 60g	54.4/100,000	11.3 [5.8-22.2]

more than 60 g	129.1/100,000	21.7 [10.8-43.5]

[a] Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 12g for example can correspond with one year of treatment with 50 mg/day for 20 days each month.

5.2 Pharmacokinetic properties

Following oral administration of tablets, cyproterone acetate is quickly and completely absorbed over a wide dosage range. The absolute bioavailability of cyproterone acetate is almost complete. The maximal plasma levels after a single dose are achieved after about 3 hours. After oral administration of

100 mg daily the steady state plasma concentration is 260 ± 50 ng/ml. The mean plasma half life is about 2 days.

Cyproterone acetate is metabolised by hydrolysis to free cyproterone, and then to 15 β-hydroxycyproterone. Excretion occurs via the bile (70%) and urine (30%). Only small amounts of unchanged drug are found in the bile, most is excreted in the form of metabolites.

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 pharmacockinetics of cyproterone acetate.

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. One *in vivo* consequence of cyproterone acetate treatment was 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 the transgenic rats carrying a bacterial gene as a target for mutation. The clinical relevance of these findings is presently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man.

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, pregelatinised maize starch, povidone, magnesium stearate, colloidal anhydrous silica.

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25ºC. Store in original package. Keep blisters in the outer carton.

6.5 Nature and contents of container

PVC/PVdC – aluminium foil blisters containing 84 tablets.

6.6 Special precautions for disposal

No special requirement for disposal

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited, 2nd Floor, Connect 38, 1 Dover Place, Ashford, Kent, England, TN23 1FB.

8 MARKETING AUTHORISATION NUMBER(S)

PL 51463/0006

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