SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate Tablets 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of Cyproterone acetate.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

For reduction of drive in sexual deviations in men, cyproterone acetate 50 mg can be used when other interventions are considered inappropriate.

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.

Control of libido in severe hypersexuality and/or sexual deviation.
The duration of cyproterone acetate treatment should be defined on an individual basis. When a satisfactory result has been achieved, the therapeutic effect should be maintained with the lowest possible dose. When changing the dose or when discontinuing cyproterone acetate, this should be done gradually

Adults and the elderly
The usual dose is 1 tablet twice daily. The daily dose should be divided and taken after the morning and evening meals.

Children (under 18 years old)
Not recommended.

The management of patients with prostatic cancer
Adults and the elderly
To suppress "flare" with initial LHRH analogue therapy
300 mg /day which may be reduced to 200 mg if the higher dose is not tolerated.

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

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 – 150 mg/day.

Children
Not recommended.

4.3 Contraindications

Cyproterone acetate is contraindicated for use in patients with liver diseases; malignant tumours (other than prostatic cancer); 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 those whose bone maturation and testicular maturation is incomplete. Patients known to be hypersensitive to cyproterone acetate or to any of the ingredients of the Cyproterone Acetate Tablets or with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Cyproterone acetate must not be used in patients with meningioma or a history of meningioma.

4.4 Special warnings and precautions for use

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

cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever hepatotoxicity is confirmed, cyproterone acetate should normally 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.

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 increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes.

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 pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats. The clinical relevance of these findings is presently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man.

Adrenocortical function: During treatment adrenocortical function should be supervised, since suppression has been observed.

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

Chronic Alcoholism: The chronic abuse of alcohol appears to reduce the effect of cyproterone acetate in male hypersexuality but the relevance of this to the treatment of prostatic cancer is not known.

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

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

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 decline in spermatogenesis is slow and cyproterone acetate should not be regarded as a male contraceptive.

Meningioma:
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 with Cyproterone Acetate Tablets 50 mg is diagnosed with meningioma, treatment with Cyproterone Acetate Tablets 50 mg 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.

Doctors are advised that fully informed consent of the patient to cyproterone acetate treatment is obtained and can be verified.

4.5 Interactions with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Not applicable. Cyproterone acetate is not indicated for use in women.

4.7 Effects on ability to drive and use machines

Marked lassitude and asthenia may be experienced particularly during the first few weeks of treatment, this necessitates especial care when driving or operating machinery.

4.8 Undesirable effects

Cyproterone acetate has been found to cause liver abnormalities in animals, including the development of tumours. Disturbances of liver function, some of them severe, have been reported with high-dose cyproterone acetate treatment. Liver function tests should be performed regularly during treatment.

In rare cases benign and in even rarer cases malignant 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.

Inhibition of spermatogenesis. The 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.

Thromboembolism: Patients with a history of thrombosis 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.

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 whilst taking cyproterone acetate therapy.

Tiredness: Fatigue and lassitude are common in the first few weeks of treatment but become less from the third month.

Breathlessness: A sensation of shortness of breath may occur under high-dose treatment with cyproterone acetate, owing to the know stimulatory effect of progesterone and synthetic progestogens on breathing, which is accompanied by hypocapnia and compensatory alkalosis, and is not considered to require treatment.

Gynaecomastia: Some patients develop transient or perhaps in some cases permanent enlargement of the mammary glands. In rare cases galactorrhoea and tender benign nodules have been reported. Symptoms mostly subside after discontinuation of treatment or reduction of dosage, but this should be weighed against the risk to the tumour of using inadequate doses.

Bodyweight: During long-term treatment, changes in body weight have been reported. Both increases and decreases have been seen.

Other changes that have been reported include reduction of sebum production and consequently improvement of existing acne vulgaris, 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.

Rarely, cases of osteoporosis have been reported.

Meningioma (frequency rare)
The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate (see section 4.4).

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, which is, therefore, generally unnecessary to treat. There are no special antidotes and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cyproterone acetate is a synthetic steroid possessing anti-androgenic and progestational activity.

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

Cyproterone has been reported as being quickly and completely absorbed from tablets. After oral administration, cyproterone acetate plasma levels peaked after 2.85 ± 0.69 hours and declined afterwards bi-phasically. Terminal half-life was reported as being 3.56 ± 1.25 days. It has a long elimination half-life resulting in steady state only being reached after 9 to 10 days on one daily dosage.

There is an active metabolite, 5 hydroxy cyproterone acetate and this attains higher levels than the parent. It has the same elimination half-life and is therefore probably formation rate controlled.

5.3 Preclinical safety data

Most of the effects of cyproterone acetate following repeat dose administration to laboratory species are related to the anti-androgenic and progestational actions of the drug. High dose levels of cyproterone acetate are embryotoxic before implantation whereas low doses have delayed effects on embryonic development. In rat studies the compound is an inducer of liver enzymes and in rat carcinogenicity studies it was associated with increased incidences of hepatocellular adenoma. In long-term tests in mice, cyproterone acetate has been associated with increased incidences of mammary gland adenocarcinoma in females. The increased tumour incidences in mice and rats may be due to the tumour promoting action of the compound, although recent evidence suggests that it may also possess direct genotoxic actions in both *in vitro* and *in vivo* test systems.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet contains lactose BP, maize starch BP, povidone BP, colloidal silicon dioxide BP and magnesium stearate BP.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at a temperature not exceeding 25°C and protect from light.

6.5 Nature and contents of container

Polyvinylchloride blisters sealed onto aluminium foil in packs of 56, 84 or 168 tablets.

Polypropylene pots with polyethylene caps and polyethylene ullage filler in packs of 100, 250 or 500 tablets.

6.6 Instructions for use/handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Generics (U.K.) Limited T/A Viatris,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER

PL 04569/0278

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/09/2005

10 DATE OF REVISION OF THE TEXT

08/05/2026