Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate Tablets 50 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cyproterone Acetate 50 mg.

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 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 contra-indicated, 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 adminstration

For oral administration only.

Control of libido in severe hypersexuality and/or sexual deviation

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: 300mg/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 – 300mg/day.

In the treatment of hot flushes in patients under treatment with LHRH analogues or who have had an orchidectomy: 50mg starting dose with upward titration if necessary within the range 50 – 150mg/day.

Children (under 18 years old): Not recommended.

4.3 Contraindications

Cyproterone acetate is contraindicated for use in patients with: liver disease; 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.

4.4 Special warnings and special 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 – 300mg 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 any symptoms or signs suggestive of hepatotoxicity occur. If 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 rates 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 balance: 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.

Doctors are advised that fully informed consent of the patient to Cyproterone Acetate treatment should be obtained and be verified.

4.5 Interaction 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.

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 special 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 are 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.

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 known 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.

4.9 Overdose

There have been no reports of ill effects from overdosage, which it 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.

5.2 Pharmacokinetic properties

Cyproterone Acetate 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 biphasically. 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 once daily dosage.

There is an active metabolite, 15-hydroxycyproterone 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 a 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

Lactose
Maize starch
Povidone (K29-32)
Colloidal silicon dioxide
Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf Life

Shelf-life of packaged product: 2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister strips

Polyvinylchloride blisters sealed onto aluminium foil.

Pack sizes: 56, 84 and 168 tablets.

Tablet containers

Polypropylene tablet containers with polyethylene caps and polyethylene ullage filler.

Pack sizes: 100, 250 and 500 tablets.

6.6 Instructions for use and handling

None.

7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited
Station Close
Potters Bar
Hertfordshire EN6 1TL
England

8 MARKETING AUTHORISATION NUMBER

PA 405/32/1

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