PROFESSIONAL INFORMATION for CIPLA-CYPROTERONE ACETATE 50

Scheduling Status

S4

Proprietary Name (and dosage form)

CIPLA-CYPROTERONE ACETATE 50 (tablets)

Composition

Each tablet contains 50 mg cyproterone acetate.

Pharmacological Classification

A 21.12 Hormone inhibitors

Pharmacological Action

The active substance cyproterone acetate is an androgen antagonist.

By means of competitive inhibition cyproterone acetate blocks androgen receptors, thereby blocking the effects of both endogenously produced and exogenously administered androgens at the target organs. The stimulating effect of the male sex hormones on androgen dependent structures, functions and pathological conditions is weakened or abolished by cyproterone acetate.

CIPLA-CYPROTERONE ACETATE 50 also possesses a progestogenic effect

and an antigonadotropic effect. Due to the negative feedback the inherent progestogenic activity has on the hypothalamic receptors, gonadotropin release is reduced, which then leads to reduced production of androgens.

Pharmacokinetics

Cyproterone acetate is slowly absorbed from the gastro-intestinal tract with peak plasma concentrations being achieved in 3 to 4 hours. The terminal elimination half-life is about 38 hours. Cyproterone is metabolised in the liver. The principal metabolite, 15 ß – hydroxycyproterone, has antiandrogenic activity. About 35% of a dose is excreted in the urine as free and conjugated metabolites and the remainder is excreted in the faeces.

Indications

In males

- Reduction of libido in sexual deviations.
- Anti-androgenic treatment in cases of inoperable carcinoma of the prostate.

In women

CIPLA-CYPROTERONE ACETATE 50 is indicated for the treatment of severe signs of androgenisation, e.g.

- androgen-dependent loss of scalp hair eventually resulting in baldness (severe androgenic alopecia)
- very severe hirsutism

- severe forms of acne and/or seborrhoea.

Contraindications

CIPLA-CYPROTERONE ACETATE 50 is contraindicated in pregnancy and lactation.

Cyproterone is also contraindicated in the following conditions:

- severe chronic depression,
- severe diabetes with vascular changes,
- Dubin-Johnson syndrome,
- history of herpes gestationis,
- history of persistent itching or jaundice during a previous pregnancy,
- acute liver diseases,
- previous or existing liver tumour (only if these are not due to metastases when used for prostate carcinoma),
- malignant tumours and wasting diseases (except prostate carcinoma),
- Rotor syndrome,
- sickle cell anaemia, and
- a history of or existing thrombosis or embolism.

It may delay bone maturation and testicular development and should therefore not be given to immature youths under 18 years or to those whose bone maturation and testicular development are incomplete.

When used in patients with prostatic carcinoma who have a history of thromboembolic processes and/or existing sickle-cell anaemia, or diabetes with vascular changes, the risk versus the benefit in each individual case must be carefully considered before initiating therapy with CIPLA-CYPROTERONE ACETATE 50.

Dosage and directions for use

The doctor will individualize dosage according to the response of each case. The tablets should be taken with a little liquid after meals.

In males

Reduction of libido in sexual deviations

Recommended dose: Generally, treatment is started with 50 mg (1 tablet) twice daily. It may be necessary to increase the dose to 100 mg (2 tablets) twice daily, or even 100 mg (2 tablets) three times daily for a short period of time.

Maintenance dose: When a satisfactory response has been achieved, one should try to maintain the therapeutic effect with the lowest possible dose. Some patients may be adequately controlled on 50mg once daily. When establishing maintenance or discontinuing the preparation, the dosage should be reduced gradually. The daily dose should be reduced by 1 tablet, or better even, half a tablet, at intervals of several weeks.

In stabilizing the therapeutic effect, it is necessary to take CIPLA-

CYPROTERONE ACETATE 50 over a prolonged period of time, if possible with simultaneous psychotherapy.

Antiandrogen treatment in cases of inoperable prostate carcinoma

After orchidectomy: 2 tablets once to twice daily (100 mg once daily to 100 mg BD).

Without orchidectomy: 2 tablets twice to three times daily (100 mg BD to 100mg TDS).

In both instances, it is important not to change or interrupt the treatment and dosage prescribed by the doctor after improvement or remissions have occurred.

In women

A thorough medical and gynaecological examination (including a breast examination and a cytological smear of the cervix) should be done before initiating CIPLA-CYPROTERONE ACETATE 50 therapy. Pregnancy must be excluded (see **Contraindications**).

Women of child-bearing age

These women must also be placed on a combination oral contraceptive for the total duration of CIPLA-CYPROTERONE ACETATE 50, therapy, to provide the necessary contraceptive protection and to stabilize the menstrual cycle. Adherence to the dosage and directions in the package insert of the oral contraceptive is imperative.

Before commencing CIPLA-CYPROTERONE ACETATE 50 therapy the patient must receive one complete cycle of a combination oral contraceptive.
Furthermore, it is important to employ additional non-hormonal methods (with the exception of the rhythm and temperature methods) during the first 3 weeks of the first cycle, which may be shorter than 4 weeks. Subsequent cycles are usually regular.
In the subsequent second cycle of the combination oral contraceptive which starts the very next day after completion of the first pack, CIPLA-CYPROTERONE ACETATE 50 treatment is started on the 5th day of the menstrual cycle (where the 1st day of bleeding is the 1st day of the cycle).

Dosage

Two CIPLA-CYPROTERONE ACETATE 50 tablets (100 mg), with some liquid after a meal, for ten days (i.e. from the 5th to the 14th day of the cycle).

This 10-day dosage regimen must be followed every menstrual cycle.
Women receiving the cyclical combination of CIPLA-CYPROTERONE ACETATE 50 and oral contraceptive therapy should take the tablets at the same time of the day each day. If more than 12 hours elapse from this specific dosing time, contraceptive protection may be reduced in that cycle. A missed tablet or tablets should be ignored and the two products should then be continued according to the above instructions, in order to avoid premature bleeding in this cycle.
However, an additional non-hormonal method of contraception (with the

exception of the temperature and rhythm methods) is to be employed for the rest of this particular cycle. A doctor should be consulted if bleeding fails to occur towards the end of the 28 -day cycle.

The doctor may reduce the daily dose of CIPLA-CYPROTERONE ACETATE 50 to 1 (50 mg) or half a tablet (25 mg) daily during the first 10 days of the combination cyclical treatment with the oral contraceptive preparation, should the patient improve clinically.

Postmenopausal or hysterectomised women

These patients do not require an oral contraceptive for contraception or cycle control. CIPLA-CYPROTERONE ACETATE 50 is therefore administered alone at an average dose of one to half a tablet (50 to 25 mg) once daily for 21 days, followed by a seven-day treatment - free interval.

The dosage will be determined by the severity of the condition.

Side effects and special precautions

Side effects

CIPLA-CYPROTERONE ACETATE 50 gradually restricts the man’s ability to procreate over the course of several weeks.

Cyproterone inhibits spermatogenesis, reduces the volume of ejaculate, and causes infertility. However, these effects are regained within a few months of discontinuing the therapy. In rare cases recovery may even be possible during dose reduction.

Abnormal spermatozoa may be produced.

Cyproterone acetate may lead to gynaecomastia in males (sometimes combined with tenderness of the mamillae), which may regress after withdrawal of the medication.

Galactorrhoea and benign nodules have been reported less frequently.

There have also been reports of hepatitis, jaundice, and hepatic failure, sometimes fatal, developing usually after several months of high dose cyproterone therapy (200-300 mg). Most reported cases were in men treated for prostatic cancer. Liver function tests should therefore be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. Toxicity is dose-related and usually develops several months after initiation of treatment. If cyproterone-induced hepatotoxicity occurs, treatment 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 benefit outweighs the risk.

In men with prostate cancer, it may be advisable to limit the duration of treatment.

The clinical relevance of findings relating to the risk of developing benign and malignant liver tumours in humans is presently unknown. Clinical experience to date does not support an increased incidence of hepatic tumours in man. Nor did animal studies (with rats) reveal any indication of a specific tumorigenic potential of cyproterone acetate. However, it is important to remember that sexual steroids can promote the growth of certain hormone-dependent tissues and

tumours.

In rare cases, benign and, in even rarer cases, malignant liver tumours have been associated with the use of sex steroids, to which cyproterone acetate also belongs. In isolated cases these tumours have led to life-threatening intra-abdominal haemorrhage. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be excluded in the differential diagnostic considerations.
In women, ovulation is inhibited during the combination cyclical treatment, rendering them infertile. This is essential because CIPLA-CYPROTERONE ACETATE 50 could lead to feminisation effects in the male foetus during pregnancy.
Tension and tenderness of the breasts may also occur.
Altered liver function and breathlessness may occur. Changes in bodyweight have been reported. Patients may experience alterations in hair patterns, anaemia, skin reactions and osteoporosis may occur less frequently.

Special precautions

Before initiating therapy in women, a thorough general medical and gynaecological examination (including a breast examination and a cytological smear of the cervix) should be done. Pregnancy must be excluded in women of child-bearing age (see **Contraindications**).
All relevant data contained in the package insert of the combination oral

contraceptive preparation should be adhered to. If, slight ‘unscheduled’ bleeding occurs, therapy should not be interrupted. However, if the bleeding is heavy or increases, the patient should consult her physician.
There may be initial sedation and depressive mood changes. Tiredness and diminished vitality can occur.
Patients whose occupation therefore demands great concentration (e.g. drivers, machine operators) should be advised that the initial sedative effects of CIPLA-CYPROTERONE ACETATE 50 can impair one’s ability to concentrate.

CIPLA-CYPROTERONE ACETATE 50 should be used with caution in ischemic heart disease, cerebrovascular disease, hypertension and other cardiovascular diseases. In extremely rare cases, thromboembolic events have been reported in temporal association with the use of cyproterone acetate, however, a causal relationship has not been established.

During treatment, regular blood counts are recommended since haemoglobin and red cell counts may decrease with cyproterone acetate therapy. In diabetics carbohydrate metabolism should be monitored carefully. Adrenocorticoid suppression has also been reported and adrenocortical function should be monitored regularly during treatment.

Alcohol, due to its disinhibitory activity, can diminish the libido- reducing effect of cyproterone acetate.

CIPLA-CYPROTERONE ACETATE 50 should not be given before the conclusion of puberty, since the possibility that it may affect longitudinal growth and the unstable axes of endocrine function unfavourably exists.

Known symptoms of overdosage and particulars of its treatment

See **SIDE EFFECTS AND SPECIAL PRECAUTIONS**. Treatment is supportive and symptomatic.

Identification

White, circular, flat, bevelled tablets, with a breakline on one side and plain on the other side.

Presentation

CIPLA-CYPROTERONE ACETATE 50 tablets are available in colourless, transparent PVC and aluminium foil blister strips of 10 tablets, packed in 20's or 50's.

Storage Instructions

Store below 25°C**.** Protect from light. Do not remove the blisters from the outer container until required for use.

KEEP OUT OF REACH OF CHILDREN.

Registration number

35/21.12/0293

Name and business address of applicant

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

BeIlville

7530

Date of publication of this package insert

May 2002