PACKAGE INSERTS FOR

CIPLA-LETROZOLE 2.5 TABLETS

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-LETROZOLE 2.5 (Film-coated tablets)

COMPOSITION:

Each film-coated tablet contains 2,5 mg letrozole.

Inactive ingredients include lactose monohydrate, sodium starch glycollate, microcrystalline cellulose, hypromellose, colloidal silicon dioxide, magnesium stearate, and opadry yellow.

Contains lactose.

PHARMACOLOGICAL CLASSIFICATION:

A 21.12 Hormone inhibitors.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme. Eliminating the oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens – primarily androstenedione and testosterone – to oestrone (E1) and oestradiol (E2).

Pharmacokinetic properties:

Absorption:

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99,9 %). Food slightly decreases the rate of absorption but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken without regard to mealtimes.

Distribution:

Plasma protein binding of letrozole is approximately 60 %, mainly to albumin (55 %). The concentration of letrozole in erythrocytes is about 80 % of that in plasma. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1,87 ± 0,47 ℓ/kg.

Metabolism and elimination:

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (Cl_m = 2,1 ℓ/h) but is relatively slow when compared

to hepatic blood flow (about 90 ℓ/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2,5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2,5 mg, while they are 1,5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2,5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs. Age had no effect on the pharmacokinetics of
letrozole.

INDICATIONS:

CIPLA-LETROZOLE is indicated in the following:

- Extended adjuvant treatment of early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with antioestrogens.

- Preoperative therapy in postmenopausal women with localised hormone receptor positive breast cancer to allow subsequent breast-conserving surgery in women not originally considered candidates for this type of surgery.

  Subsequent treatment after surgery should be in accordance with standard of care.

CONTRA-INDICATIONS:

CIPLA-LETROZOLE is contra-indicated in the following:

- Hypersensitivity to the active substance or to any of the excipients.
- Premenopausal endocrine status.
- Pregnancy or lactation.
- Severe impairment of hepatic function (Child-Pugh grade C).
- Severe impairment of renal function (creatinine clearance < 10 mℓ/min).

WARNINGS:

Hepatic function impairment:

Although modest increments in letrozole blood concentration have been observed in individuals with hepatic function impairment due to cirrhosis, no dosage adjustments are recommended in mild to moderate hepatic function impairment. In patients with severe hepatic impairment (Child-Pugh grade C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers (see **"CONTRA-INDICATIONS"**).

INTERACTIONS:

Co-administration of **CIPLA-LETROZOLE** with cimetidine and warfarin does not result in clinically significant interactions.

Letrozole inhibits *in vitro* the cytochrome P450-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in medicine metabolism. In *in vitro* experiments letrozole was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of medicines whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

In postmenopausal women with breast cancer, the addition of tamoxifen reduced letrozole, as in **CIPLA-LETROZOLE**, plasma concentrations by a mean of about 38 %, but the effect of **CIPLA-LETROZOLE** on hormone concentrations was unchanged. The mechanism and possible clinical effect of this interaction are unknown.

There is no clinical experience to date on the use of **CIPLA-LETROZOLE** in combination with other anti-cancer agents.

PREGNANCY AND LACTATION:

The use of **CIPLA-LETROZOLE** is contra-indicated during pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE:

Adults and elderly patients:

The recommended dose of **CIPLA-LETROZOLE** is 2,5 mg once daily. In the extended adjuvant setting, treatment with **CIPLA-LETROZOLE** should continue for 5 years or until tumour relapse occurs, whichever comes first. In patients with metastatic disease, treatment with **CIPLA-LETROZOLE** should continue until tumour progression is evident.

Elderly patients:

No dose adjustment is required for elderly patients.

Children:

Not applicable.

Patients with hepatic and/or renal impairment:

Dosage adjustment is not required for patients with renal impairment (creatinine clearance ≥ 10 mℓ/min) or mild to moderate hepatic impairment (Child-Pugh grade A and B). Insufficient data are available to establish dosage recommendations for patients with a creatinine clearance of < 10 mℓ/min (see **"CONTRA-INDICATIONS"**).

CIPLA-LETROZOLE should not be used in patients with severe hepatic impairment (Child-Pugh score C) (see **"CONTRA-INDICATIONS"** and **"WARNINGS"**).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The following side-effects may occur with the use of **CIPLA-LETROZOLE**:

Infections and infestations:

Less frequent:	Urinary tract infection.

Neoplasms benign and malignant (including cysts and polyps):

Less frequent:	Tumour pain.

Blood and lymphatic system disorders:

Less frequent:	Leucopenia.

Metabolism and nutrition disorders:

Frequent:	Anorexia, appetite increase.
Less frequent:	Hypercholesterolaemia and general oedema.

Psychiatric disorders:

Less frequent:	Depression, anxiety, nervousness, and irritability.

Nervous system disorders:

Frequent:	Headache, dizziness.
Less frequent:	Somnolence, insomnia, memory impairment, dysaesthesia, taste disturbance, and cerebrovascular accident.

Eye disorders:

Less frequent:	Cataract, eye irritation, and blurred vision.

Cardiac disorders:

Less frequent:	Palpitations, tachycardia, myocardial infarction, and myocardial ischaemia.

Vascular disorders:

Less frequent:	Thrombophlebitis (superficial and deep thrombophlebitis), hypertension, pulmonary embolism, arterial thrombosis, and cerebrovascular infarction.

Respiratory, thoracic and mediastinal disorders:

Less frequent:	Dyspnoea.

Gastrointestinal disorders:

Frequent:	Nausea, vomiting, dyspepsia, constipation, and diarrhoea.
Less frequent:	Abdominal pain, stomatitis, and dry mouth.

Hepato-biliary disorders:

Less frequent:	Increased hepatic enzymes.

Skin and subcutaneous tissue disorders:

Frequent:	Alopecia, increased sweating, rash (including erythematous, maculopapular, psoriasiform and vascular rash).

Less frequent: Pruritus, dry skin, and urticaria.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia, bone pain, arthralgia, arthritis, and bone fracture.

Less frequent: Osteoporosis.

Renal and urinary disorders:

Less frequent: Increased urinary frequency.

Reproductive system and breast disorders:

Less frequent: Vaginal bleeding, vaginal discharge, vaginal dryness, and breast pain.

General disorders and administration site conditions:

Frequent: Fatigue (including asthenia and malaise), peripheral oedema, and hot flushes.

Less frequent: Pyrexia, mucosal dryness, and thirst.

Investigations:

Frequent: Weight loss.

Less frequent: Weight increase.

<u>Special Precautions:</u>

Impaired renal function:

CIPLA-LETROZOLE has not been investigated in patients with creatinine clearance < 10 mℓ/min (see **"CONTRA-INDICATIONS"**).

Reduction of bone mineral density:

Postmenopausal women with primary breast cancer were reported to have significant decreases in bone mineral density at the hip and lumbar spine after 24 months of letrozole, as in **CIPLA-LETROZOLE**, therapy. Patients with or at risk of osteoporosis should therefore have their bone density assessed at the start of therapy and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be started as appropriate and carefully monitored.

Lactose:

CIPLA-LETROZOLE contains lactose. Women who are lactose intolerant and who take **CIPLA-LETROZOLE** may experience unwanted side-effects, such as nausea, cramping, bloating, diarrhoea, and flatulence. **CIPLA-LETROZOLE** should not be taken by women with rare hereditary problems (or a history) of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machinery:

Fatigue and dizziness have been observed with the use of **CIPLA-LETROZOLE** and somnolence has been reported uncommonly. Patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There are isolated cases of overdosage with **CIPLA-LETROZOLE**, which have been reported. No specific treatment for overdosage is known; treatment should be symptomatic and supportive.

IDENTIFICATION:

CIPLA-LETROZOLE 2.5: Yellow, circular, biconvex film-coated tablets plain on both sides.

PRESENTATION:

CIPLA-LETROZOLE 2.5: Clear PVC/PE/PVDC on plain aluminium foil blister strips of 10 tablets packed in 30's.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC. Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

Keep blister in outer carton until required for use.

REGISTRATION NUMBER:

44/21.12/0282

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

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