PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

LARADEX 2,5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 2,5 mg Letrozole.

Contains 61,500 mg lactose monohydrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablets

Yellow, round, biconvex, film coated tablets, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- First-line treatment in postmenopausal women with advanced breast cancer.
- LARADEX is also indicated for the treatment of hormone-dependant advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with anti-oestrogens. Pre-operative therapy in postmenopausal women with localised oestrogen 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.

- Extended adjuvant treatment of early invasive breast cancer in post-menopausal women who have received prior standard adjuvant tamoxifen therapy for five years.

4.2 Posology and method of administration

Adults and elderly patients: The recommended dose of LARADEX is 2,5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with LARADEX should continue for 5 years or until disease relapse/recurrence occurs, whichever comes first. In patients with metastatic disease, treatment with LARADEX should continue until tumour progression is evident. In the neoadjuvant (preoperative) setting, treatment with LARADEX should be continued for 4 to 8 months in order to establish optimal tumour reduction. If the response is not adequate, treatment with LARADEX should be discontinued, surgery scheduled and/or further treatment options discussed with the patient.

No dose adjustment is required for elderly patients.

Children: Not applicable.

Patients with hepatic and/ or renal impairment: No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh grade A and B) or renal impairment (creatinine clearance >10 ml/min). Insufficient data is available to establish dosage recommendations for patients with a creatinine clearance of < 10 ml/min (see section 4.3). However, LARADEX should not be used in patients with severe hepatic impairment (Child-Pugh score C).

Method of administration

LARADEX should be taken orally and can be taken with or without food.

A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose, the missed dose should be skipped and the patient should go back to their regular dosage schedule. Doses should not be doubled, because with daily doses over 2,5 mg recommended dose, over-proportionality in systemic exposure was observed (see section 5.2).

4.3 Contraindications

- 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).
- Impairment of renal function (creatinine clearance < 10 ml/min).

4.4 Special warnings and precautions for use

Menopausal status

In patients whose menopausal status is unclear, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or oestradiol levels should be measured before initiating treatment with LARADEX. Only women of postmenopausal endocrine status should receive LARADEX.

Impaired renal function:

LARADEX has not been investigated in patients with creatinine clearance < 10 ml/min.

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers.

Bone effects

Osteoporosis and/or bone fractures have been reported with the use of LARADEX. Therefore, monitoring of overall bone health is recommended during treatment.

Fertility

The pharmacological action of LARADEX is to reduce oestrogen production by aromatase inhibition. In premenopausal women, the inhibition of oestrogen synthesis leads to feedback increases in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular growth and can induce ovulation.

Interactions

Co-administration of LARADEX with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of LARADEX (see section 4.5).

Contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take LARADEX.

4.5 Interactions with other medicines and other forms of interaction

LARADEX mainly metabolised in the liver and the cytochrome P450 enzymes CYP3A4 and CYP2A6 mediate the metabolic clearance of LARADEX. Therefore, the systemic elimination of LARADEX may be influenced by medicines known to affect the CYP3A4 and CYP2A6. The metabolism of LARADEX appears to have low affinity for CYP3A4 because the enzyme could not be saturated at concentrations more than 150-fold higher than those observed in plasma for LARADEX at steady-state in the typical clinical situation.

Medicine that may increase LARADEX serum concentrations

Inhibitors of CYP3A4 and CYP2A6 activities could decrease the metabolism of LARADEX and thereby increase plasma concentrations of LARADEX. The concomitant administration of medications that strongly inhibits these enzymes (strong CYP3A4 inhibitors: including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telithromycin; CYP2A6 (e.g. methoxsalen) may increase exposure to LARADEX. Therefore caution is recommended in patients for whom strong CYP3A4 and CYP2A6 inhibitors are administered.

Medicine that may decrease LARADEX serum concentrations

Inducers of CYP3A4 activity could increase the metabolism of LARADEX and thereby decrease plasma concentrations of LARADEX. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital and St. John's Wort) may reduce exposure to LARADEX. Therefore caution is recommended in patients for whom strong CYP3A4 inducers are administered.

Co-administration of LARADEX and tamoxifen 20 mg daily resulted in a reduction of LARADEX plasma levels by 38 % on average. Clinical experience in the second-line breast cancer trials indicates that neither the therapeutic effect of LARADEX therapy nor the occurrence of adverse reactions is increased if LARADEX is administered immediately after tamoxifen. The mechanism of this interaction is unknown.

Medicine that may have their systemic serum concentrations altered by LARADEX

In vitro, LARADEX inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving LARADEX concomitantly with medicinal products whose elimination is mainly dependent on

CYP2C19 and whose therapeutic index is narrow (e.g. phenytoin, clopidogrel). No substrate with narrow therapeutic index is known for CYP2A6.

Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of LARADEX with these medicines does not result in clinically significant interactions. Additionally, in a large clinical trial there was no evidence of clinically relevant interactions in patients receiving other commonly prescribed medicines (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole). There is no clinical experience to date on the use of LARADEX in combination with other anti-cancer agents.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

LARADEX should only be used in women with a clearly established postmenopausal status.
The doctor needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who recently became postmenopausal, until their postmenopausal status is fully established.

Pregnancy

LARADEX is contra-indicated during pregnancy.
LARADEX may cause foetal harm when administered to a pregnant woman.
The patient should be apprised of the potential risk to the foetus, if LARADEX is used during pregnancy or if the patient becomes pregnant while taking this medicine.

There are no clinical trials conducted in pregnant women with LARADEX. There have been post-marketing reports of spontaneous abortions and congenital anomalies in infants of mothers who have taken LARADEX (see section 4.3).

Cases of birth defects (labial fusion, ambiguous genitalia) have been reported in infants born to woman exposed to off label use (infertility treatment, ovulation induction) of LARADEX during pregnancy.

Lactation

LARADEX is contraindicated during lactation (see section 4.3)

It is not known if LARADEX is excreted in human milk. There are no data on the effects of LARADEX on the breastfed child or the effects of LARADEX on milk production.

4.7 Effects on ability to drive and use machines

Fatigue and dizziness have been observed with the use of LARADEX. Patients should be advised that their physical and /or mental abilities required for operating machinery or driving a car, may be impaired.

4.8 Undesirable effects

The following side effects can occur:

Infections and infestations

Less Frequent: Urinary tract infection

Neoplasms, benign, malignant and unspecified (including cysts and polyps)

Less Frequent: Tumour pain in metastatic/neoadjuvant setting

Blood and lymphatic system disorders

Less Frequent: Leucopenia

Immune system disorders

Frequency unknown: Angioedema, anaphylactic reactions

Metabolism and nutrition disorders

Frequent: Anorexia, appetite increase, raised serum cholesterol

Less Frequent: General oedema

Psychiatric disorders

Frequent: Depression

Less Frequent: Anxiety including nervousness, irritability

Nervous system disorders

Frequent: Headache, dizziness

Less Frequent: Somnolence, insomnia, memory impairment, dysaesthesia including paraesthesia, hypoaesthesia, taste disturbance, cerebrovascular accident, carpal tunnel syndrome

Eye disorders

Less Frequent: Cataract, eye irritation, blurred vision

Cardiac disorders

Less Frequent: Palpitations, tachycardia

Vascular disorders

Less Frequent: Thrombophlebitis including superficial and deep thrombophlebitis, hypertension, ischaemic cardiac events, pulmonary embolism, arterial thrombosis, cerebrovascular infarction

Respiratory, thoracic and mediastinal disorders

Less Frequent: Dyspnoea, cough

Gastrointestinal disorders

Frequent: Nausea, vomiting, dyspepsia, constipation, diarrhoea

Less Frequent: Abdominal pain, stomatitis, dry mouth

Hepatobiliary disorders

Less Frequent: Increased hepatic enzymes, hyperbilirubinaemia, jaundice

Frequency unknown: Hepatitis

Skin and subcutaneous tissue disorders

Frequent: Alopecia, increased sweating, rash including erythematous,maculopapular, psoriaform and vesicular rash

Less Frequent: Pruritus, dry skin, urticarial

Frequency unknown: Toxic epidermal necrolysis, erythema multiforme

Musculoskeletal and connective tissue disorders

Frequent: Arthralgia, myalgia, bone pain, osteoporosis, bone fractures

Less Frequent: Arthritis

Frequency unknown: Trigger finger

Renal and urinary disorders

Less Frequent: Increased urinary frequency

Reproductive system and breast disorders

Less Frequent: Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain

General disorders and administration site conditions

Frequent: Hot flushes, fatigue including aesthenia and malaise, peripheral oedema

Less Frequent: Pyrexia, mucosal dryness, thirst

Investigations

Frequent: Weight increase

Less Frequent: Weight loss

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website, or

to Eurolab (Pty) Ltd. by email: drug-safety@eurolab.co.za. By reporting side effects, you can help provide more information on the safety of LARADEX.

4.9 Overdose

No specific treatment for overdosage is known; treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.12 Hormone inhibitors

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. Letrozole is specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH or in plasma renin activity amongst postmenopausal patients.

5.2 Pharmacokinetic properties

Absorption: Letrozole is rapidly and completely absorbed from the gastro-intestinal 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 mealtime.

Distribution:

Plasma protein binding of letrozole is approximately 60 %, mainly to albumin (55 %). The concentrations of letrozole in erythrocytes are about 80 % of that in plasma. After administration of 2,5 mg ^{14}C-labelled letrozole, approximately 82 % of the radioactivity in plasma was an unchanged compound. Systemic exposure to metabolites is therefore low. 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. Within 2 weeks after administrations of 2,5 mg 14C-labelled letrozole to healthy postmenopausal volunteers, 88,2 ± 7,6 % of the radioactivity was recovered in urine and 3,8 ± 0,9 % in faeces. At least 75 % of the radioactivity recovered in urine up to 216 hours (84,7 ± 7,8 % of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9 % to two unidentified metabolites and 6 % to unchanged 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 has no effect on the pharmacokinetics of letrozole.

Special populations:

In a study involving volunteers with varying degrees of renal function (24 hour creatinine clearance 9 to 116 ml/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2,5 mg. In a similar study involving subjects with varying degrees of hepatic functions, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37 % higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose of 2,5 mg letrozole in eight subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (N=8), AUC and T1/2 increased by 95 % and 187 %, respectively. Breast cancer patients with severe hepatic impairment are thus exposed to higher levels of letrozole than patients without severe hepatic dysfunction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Hydroxypropyl methylcellulose

Iron oxide yellow

Lactose monohydrate.

Magnesium stearate

Maize starch

Microcrystalline cellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Do not remove the blisters from the outer container until required for use.

6.5 Nature and contents of container

LARADEX film coated tablets are packed in plain aluminum blister strips of 10 tablets per strip, with a clear PVC coated PVDC film.

3 strips of 10 tablets (30 tablets) are packed in a unit carton.

6.6 Special precautions for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park

3 Stirrup Lane, Van Reenans Avenue

Woodmead

Gauteng

South Africa

8 REGISTRATION NUMBER

LARADEX: 42/21.12/0324

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 November 2010

10 DATE OF REVISION OF THE TEXT

10 March 2025