PACKAGE INSERT TEMPLATE FOR LETROZOLE TABLET

Brand or Product Name
[Product name] Tablet 2.5mg

Name and Strength of Active Substance(s)
Letrozole 2.5mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)]
eg White, circular flat beveled edge tablets marked '2.5' on one side

Pharmacodynamics

The growth of some cancers of the breast is stimulated or maintained by estrogens. The elimination of 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, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to oestrone (E1) and oestradiol (E2).. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme. As a result, letrozole interferes with estrogen-induced stimulation or maintenance of growth of hormonally responsive (estrogen and/or progesterone receptor positive or receptor unknown) breast cancers.

Letrozole is a non-steroidal aromatase inhibitor and is highly specific in inhibiting aromatase activity. It inhibits the aromatase enzyme by competitively binding to the haem group of aromatase, a cytochrome P450 enzyme which catalyzes conversion of androgens to estrogens (specifically, androstenedione to estrone and testosterone to estradiol) resulting in a significant reduction of oestrogen biosynthesis in peripheral tissues and cancer tissue. Aromatase inhibition by letrozole appears to be specific, with sparing of other cytochrome P450 enzymes of the same class involved in glucocorticoid and mineralocorticoid synthesis

There is no changes in plasma concentrations of androgens (androstenedione and testosterone) or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of letrozole indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor are thyroid function as evaluated by TSH, T4 and T3 uptake.

Pharmacokinetics

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract. Food decreases the rate but not the extent of absorption.

Distribution

Letrozole is rapidly and extensively distributed to tissues.

Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%).

Its apparent volume of distribution at steady state is about 1.87 ± 0.47 L/kg.

Metabolism and elimination

In vitro data suggest that it is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2A6. Most of an oral dose is slowly metabolised to an inactive carbinol metabolite, which is then excreted as the glucuronide in the urine. Letrozole has a terminal elimination half-life of about 2 days, and steady-state concentrations occur within 2 to 6 weeks.

Age had no effect on the pharmacokinetics of letrozole.

Indication

•Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

• Adjuvant treatment of postmenopausal women with early breast cancer (positive or unknown oestrogen or progesterone receptor status) who have received 5 years of adjuvant tamoxifen therapy (extended adjuvant 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.

• Pre-operative therapy in postmenopausal women with localized 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.

Recommended Dosage

Adult and elderly patients

The recommended dose of Letrozole is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with Letrozole should continue for 5 years or until tumor relapse occurs, whichever comes first. In patients with metastatic disease, treatment with Letrozole should continue until tumor progression is evident. 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 hepatic impairment or renal impairment (creatinine clearance =10 mL/min.). However, patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision

Mode of Administration
Oral

Contraindications

• Known hypersensitivity to the active substance or to any of the excipients.
• Premenopausal endocrine status; pregnancy, lactation

Warnings and Precautions

Renal impairment

Letrozole has not been investigated in patients with creatinine clearance <10 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of Letrozole.

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. Such patients should therefore be kept under close supervision.

Bone effects

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

Effects on Ability to Drive and Use Machines

Since fatigue and dizziness have been observed with the use of Letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines.

Interactions with Other Medicaments

There is no clinically significant drug interactions from coadministration of letrozole with cimetidine and warfarin .

There is no evidence of clinically relevant interactions with other commonly prescribed drugs.

There is no clinical experience on the use of letrozole in combination with other anticancer agents.

Letrozole inhibits in vitro the cytochrome P450-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in drug metabolism. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

Concurrent use of letrozole and tamoxifen may result in reduced letrozole serum concentrations.

Statement on Usage During Pregnancy and Lactation

Pregnancy

Letrozole is contraindicated during pregnancy.

Women of perimenopausal status or child-bearing potential

The physician 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

Lactation

Letrozole is contraindicated during lactation

Adverse Effects / Undesirable Effects

Letrozole is generally well tolerated as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer and as extended adjuvant treatment in women who have received prior standard tamoxifen therapy.
Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with estrogen deprivation.

The most frequently reported adverse reactions were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of estrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

System Organ Class

Infections and Infestations

Uncommon: Urinary tract Infection

Benign, Malignant and Unspecified Neoplasms (including cysts and polyps)

Uncommon: Tumor pain (metastatic/neoadjuvant)

Blood and Lymphatic System Disorders

Common: Leukopenia

Metabolism and Nutrition Disorders
Common: Anorexia, increased appetite, hypercholesterolemia
Uncommon: General oedema.

Psychiatric Disorders

Common: Depression Uncommon: Anxiety including nervousness and irritability.

Nervous System Disorders

Common: Headache, dizziness Uncommon: Somnolence, memory impairment, dysaesthesia including paraesthesia and hypoesthesia, taste disturbance, cerebrovascular accident

Eye Disorders

Uncommon: Cataract, eye irritation, blurred vision

Cardiac Disorders

Uncommon: Palpitations, tachycardia

Vascular Disorders

Uncommon: Thrombophlebitis including superficial and deep, hypertension, ischaemic cardiac events (the adjuvant setting, irrespective of causality, the following adverse events occurred in the Letrozole and tamoxifen groups, respectively: Thromboembolic events, angina pectoris, myocardial infarction and cardiac failure.
Rare: Pulmonary embolism, arterial thrombosis, cerebrovascular infarction

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: Dyspnoea

Gastrointestinal Disorders

Common: Nausea, vomiting, dyspepsia, constipation, diarrhoea,
Uncommon: Abdominal pain, stomatitis, dry mouth.

Hepatobiliary Disorders

Uncommon: Increased hepatic enzymes

Skin and Subcutaneous tissue Disorders

Common: Alopecia increased sweating, rash including erythematous, maculopapular, psoriaform and vesicular rash.
Uncommon: Pruritis, dry skin, urticaria

Musculoskeletal, Connective Tissue and Bone Disorders

Very common: Arthralgia Common: Myalgia, bone pain, osteoporosis, bone fractures, arthritis

Renal and Urinary Disorders

Uncommon: Increased urinary frequency

Reproductive System and Breast Disorders

Uncommon: Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain

General Disorders and Administration Site Conditions

Very common: Hot flushes Common: Fatigue including asthenia and malaise, peripheral oedema
Uncommon: Pyrexia, mucosal dryness, thirst

Investigations

Common: Increased weight
Uncommon: Weight loss

Overdose and Treatment

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

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]