SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LETRAZ (2,5 mg, Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, round biconvex, film coated tablets. Debossed “2,5” on one side, plain on reverse side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.
- 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 a natural or artificially induced postmenopausal status, who have previously been treated with anti-oestrogen therapy.
- Pre-operative 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 care.

4.2 Posology and method of administration

Posology

Adults and elderly patients:

The recommended dose of LETRAZ is 2,5 mg once daily by mouth.

In the adjuvant and extended adjuvant setting, treatment with LETRAZ is given for 5 years or until tumour relapse occurs, whichever comes first.

Where metastatic disease occurs, treatment with LETRAZ should continue until tumour progression is evident.

Method of administration

Oral.

Elderly patients:

No dose adjustment is required for geriatric patients.

Paediatric patients:

Not suitable for use in children.

Patients with hepatic and/or renal impairment:

No dosage adjustment is recommended for patients with mild to moderate hepatic function impairment (Child Pugh grade A and B) or renal function impairment (creatinine clearance ≥ 10 ml/min).

Insufficient data are available to establish dosage recommendations for patients with a creatinine clearance of < 10 ml/min (see section 4.3).

LETRAZ should not be used in patients with severe hepatic impairment (Child-Pugh score C) (see section 4.3).

4.3 Contraindications

- Hypersensitivity to the active substance, letrozole, or to any of the excipients, see section 6.1.
- Premenopausal women.
- Pregnancy and lactation.
- Severe hepatic function impairment (Child-Pugh grade C).

- Severe renal function impairment (creatinine clearance < 10 ml/min).

4.4 Special warnings and precautions for use

Reductions in bone mineral density can occur during treatment with LETRAZ. This effect may increase the risk of bone fractures, especially in patients with osteoporosis. Patients with or at risk of osteoporosis should 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.

No data are available in patients with a creatinine clearance of < 10 ml/min (see section 4.3).

An increased incidence of cardiovascular adverse effects has been seen in woman with pre-existing ischaemic heart disease and caution is advised in these patients.

In patient with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

LETRAZ inhibits *in vitro* the cytochrome P450-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in the metabolism of LETRAZ. 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.

The co-administration of LETRAZ with the following commonly prescribed medicines does not result in clinically significant interactions: cimetidine, warfarin, benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole.

Concomitant administration of tamoxifen may reduce plasma concentrations of LETRAZ.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of LETRAZ is contraindicated during pregnancy (see section 4.3).

Breastfeeding

The use of LETRAZ is contraindicated during breastfeeding (see section 4.3).

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

Since fatigue, dizziness and somnolence may occur when using LETRAZ, caution is advised when driving or using machines.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent side effects with LETRAZ are hot flushes, nausea and fatigue.

b) Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Undesirable effect**
Infections and infestations	*Less frequent*	Urinary tract infections
Neoplasms benign and malignant (including cysts and polyps)	*Less frequent*	Tumour pain in metastatic/neoadjuvant setting only
Blood and lymphatic system disorders	*Less frequent*	Leukopenia
Immune system disorders	*Less frequent*	Anaphylaxis, angioedema
Metabolism and nutrition disorders	*Frequent*	Anorexia, appetite increase, hypercholesterolaemia, hypercalcaemia
	Less frequent	General oedema
Psychiatric disorders	*Frequent*	Depression
	Less frequent	Anxiety, including nervousness and irritability
Nervous system disorders	*Frequent*	Headache, dizziness

	Less frequent	Somnolence, insomnia, memory impairment, dysaesthesia including paraesthesia and hypoaesthesia, taste disturbance, cerebrovascular accident
Eye disorders	*Less frequent*	Cataract, eye irritation, blurred vision
Cardiac disorders*	*Less frequent*	Palpitations, tachycardia, cardiac failure, angina pectoris, ischaemic cardiac events
Vascular disorders	*Less frequent*	Superficial and deep thrombophlebitis including superficial and deep thrombophlebitis, hypertension, 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
Hepato-biliary disorders	*Less frequent*	Increased hepatic enzymes, hepatitis
Skin and subcutaneous tissue disorders	*Frequent*	Alopecia, increased sweating, rash including erythematous, macupapular, psoriaform and vesicular rash.
	Less frequent	Pruritus, dry skin, urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Arthralgia, myalgia, bone pain, osteoporosis, bone fractures
	Less frequent	Arthritis, decreased bone mineral density
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 administrative site conditions	*Frequent*	Hot flushes, fatigue, including asthenia and malaise, peripheral oedema
	Less frequent	Pyrexia, mucosal dryness, thirst
Investigations	*Frequent*	Weight increase
	Less frequent	Weight loss

c) Description of selected adverse reactions

***** In the adjuvant setting, irrespective of causality, the following adverse events occurred in the LETRAZ and tamoxifen groups respectively: thromboembolic events, angina pectoris, myocardial infarction and cardiac failure.

4.9 Overdose

Treatment is symptomatic and supportive. There is no specific treatment for overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.12 Hormone Inhibitors.

Letrozole is a non-steroidal competitive inhibitor of aromatase and is specific in inhibiting aromatase activity by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues. In postmenopausal women, letrozole inhibits conversion of adrenal androgens (primarily androstenedione and testosterone) to oestrogens (oestrone and oestradiol) in peripheral tissues and cancer tissues. As a result, letrozole interferes with oestrogen-induced stimulation or maintenance of growth of breast cancers.

Where the growth of tumour tissues depends on the presence of oestrogens, the elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response.

5.2 Pharmacokinetic properties

Letrozole is completely and rapidly absorbed from the gastrointestinal tract. The rate of absorption is slightly decreased by food, but the extent of absorption is not changed. About 60 % of letrozole circulation is bound to plasma protein, mainly to albumin. Letrozole is rapidly and extensively distributed to tissues.

Most of an oral dose is slowly metabolised to an inactive carbinol metabolite and its ketone analogue by the CYP isoenzymes 3A4 and 2A6 (CYP 3A4 and CYP 2A6).

About 90 % of a dose is excreted in the urine (75 % is excreted as the glucuronide conjugate of the inactive metabolite, 9 % as two unidentified metabolites, and 6 % as unchanged letrozole).

Letrozole has a terminal elimination half-life of about 2 days. The time to steady-state concentrations in the plasma is 2 to 6 weeks, which are 1,5 to 2 times higher than would be predicted on the basis of single-dose measurements, indicating some non-linearity in letrozole's pharmacokinetics with daily administration.

However steady-state concentrations are maintained for extended periods, without further accumulation of letrozole.

The pharmacokinetics of letrozole is not affected by age.

Special populations

In patients 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 patients with varying degrees of hepatic function, 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.

After a single dose of letrozole in patients with liver cirrhosis and severe hepatic impairment (Child-Pugh score C), there is a 95 % increase in the AUC and a 187 % increase in the $t_{½}$. 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

Magnesium stearate

Polyethylene glycol

Polyvinyl alcohol

Silicified microcrystalline cellulose

Sodium starch glycollate

Sunset yellow FCF

Talc

Titanium dioxide

Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove blisters from outer container until required for use.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clear PVC/PVdC silver aluminium blister strips packed in an outer carton. Each blister strip contains 10 film-coated tablets. 30 Tablets per outer carton.

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria

8. REGISTRATION NUMBER

45/21.12/0544

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 10 October 2013

10. DATE OF REVISION OF THE TEXT

06 May 2022