SUMMARY OF PRODUCT CHARACTERISTICS

LETRODAY 2.5

Letrozole Tablets 2.5 mg

Rx Only

NAME OF THE PRODUCT : Letrozole Tablets 2.5 mg

(TRADE) NAME OF PRODUCT : LETRODAY 2.5

STRENGTH:2.5 mg

PHAPMACEUTICAL DOSAGE FORM: Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Each film-coated tablet contains:

Letrozole Ph.Eur …… 2.5 mg

PHARMACEUTICAL FORM

Letrozole Tablets 2.5 mg

Dark yellow, film coated,round,slightly biconvex, with beveled edges tablet debossed with 'L2.5' on one side and plain on the other side.

CLINICAL PARTICULARS

Therapeutic indications

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Advanced breast cancer after relapse or disease progression, in women with natural or artificially inducedpostmenopausal endocrine status, who have previously been treated with anti-oestrogens.
- Neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancerwhere chemotherapy is not suitable and immediate surgery not indicated.

Efficacy has not been demonstrated in patients with hormone receptor negative breast cancer.

Posology and method of administration

Posology

Adult and elderly patients

The recommended dose of Letrozole is 2.5 mg once daily. No dose adjustment is required for elderly patients.

In patients with advanced or metastatic breast cancer, treatment with Letrozole should continue until tumour progression isevident.

In the adjuvant and extended adjuvant setting, treatment with Letrozole should continue for 5 years or until tumour relapseoccurs, whichever is first.

In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also beconsidered.

In the neoadjuvant setting, treatment with Letrozole could be continued for 4 to 8 months in order to establish optimaltumour reduction. If the response is not adequate, treatment with Letrozole should be discontinued and surgery scheduledand/or further treatment options discussed with the patient.

Paediatric population

Letrozole is not recommended for use in children and adolescents. The safety and efficacy of Letrozole in children andadolescents aged up to 17 years have not been established. Limited data are available and no recommendation on aposology can be made.

Renal impairment

No dosage adjustment of Letrozole is required for patients with renal insufficiency with creatinine clearance ≥10 ml/min.

Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 10 ml/min.

Hepatic impairment

No dose adjustment of Letrozole is required for patients with mild to moderate hepatic insufficiency (Child-Pugh A or B).

Insufficient data are available for patients with severe hepatic impairment. Patients with severe hepatic impairment(Child-Pugh C) require close supervision.

Method of administration

Letrozole 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 (within2 or 3 hours), the missed dose should be skipped, and the patient should go back to her regular dosage schedule.

Doses should not be doubled because with daily doses over the 2.5 mg recommended dose, over-proportionality insystemic exposure was observed.

Contraindications

• Hypersensitivity to the active substance or to any of the Excipients.

• Premenopausal endocrine status

• Pregnancy

• Breast-feeding

Special warnings and precautions for use

Menopausal status

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

Renal impairment

Letrozole has not been investigated in a sufficient number of patients with a creatinine clearance lower than 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 C), systemic exposure and terminal half-life were approximatelydoubled compared to healthy volunteers. Such patients should therefore be kept under close supervision.

Bone effects

Letrozole is a potent oestrogen-lowering agent. Women with a history of osteoporosis and/or fractures, or who are atincreased risk of osteoporosis, should have their bone mineral density formally assessed prior to the commencement ofadjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole. Treatment orprophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. In the adjuvant setting a

sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered depending onthe patient's safety profile.

Other warnings

Co-administration of Letrozole with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoidedas these substances may diminish the pharmacological action of letrozole.

As the tablets contain lactose, Letrozole is not recommended for patients with rare hereditary problems of galactoseintolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

Interaction with other medicinal products and other forms of interaction

Metabolism of letrozole is partly mediated via CYP2A6 and CYP3A4. Cimetidine, a weak, unspecific inhibitor of CYP450enzymes, did not affect the plasma concentrations of letrozole. The effect of potent CYP450 inhibitors is unknown.

There is no clinical experience to date on the use of Letrozole in combination with oestrogens or other anticancer agents,other than tamoxifen. Tamoxifen, other anti-oestrogens or oestrogen-containing therapies may diminish thepharmacological action of letrozole. In addition, co-administration of tamoxifen with letrozole has been shown tosubstantially decrease plasma concentrations of letrozole. Co-administration of letrozole with tamoxifen, other antioestrogens

or oestrogens should be avoided.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance isunknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose eliminationis mainly dependent on these isoenzymes and whose therapeutic index is narrow (e.g. phenytoin, clopidrogel).

Fertility, pregnancy and lactation

Women of perimenopausal status or child-bearing potential

Letrozole should only be used in women with a clearly established postmenopausal status. Women may regainovarian function during treatment with Letrozole despite a clear postmenopausal status atstart of therapy, the physician needs to discuss adequate contraception when necessary.

Pregnancy

Letrozole may cause congenital malformations when administered during pregnancy. Studies in animals haveshown reproductive toxicity.

Letrozole is contraindicated during pregnancy.

Breast-feeding

It is unknown whether letrozole and its metabolites are excreted in human milk. A risk to the newborns/infants cannot beexcluded.

Letrozole is contraindicated during breast-feeding.

Fertility

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

Effects on ability to drive and use machines

Letrozole has minor influence on the ability to drive and use machines. Since fatigue and dizziness may be observed with the use of Letrozole and somnolence may occur uncommonly, caution is advised when driving or usingmachines.

Undesirable effects

The most frequently reported adverse reactions are hot flushes, hypercholesterolaemia, arthralgia,fatigue, increased sweating and nausea.

Important additional adverse reactions that may occur with Letrozole are: skeletal events such as osteoporosis and/orbone fractures and cardiovascular events (including cerebrovascular and thromboembolic events).

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: verycommon (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare(<1/10,000); not known (cannot be estimated from the available data).

Infections and infestations	
Uncommon:	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Tumour pain[1]
Blood and lymphatic system disorders	
Uncommon:	Leukopenia
Immune system disorders	
Not known:	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common:	Hypercholesterolaemia
Common:	Decreased appetite, increased appetite
Psychiatric disorders	
Common:	Depression
Uncommon:	Anxiety (including nervousness), irritability
Nervous system disorders	
Common:	Headache, dizziness
Uncommon:	Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia),dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Common:	Palpitations[1]
Uncommon:	Tachycardia, ischaemic cardiac events (including new or worsening angina, angina requiringsurgery, myocardial infarction and myocardial ischaemia)
Vascular disorders	
Very common:	Hot flushes
Common:	Hypertension
Uncommon:	Thrombophlebitis (including superficial and deep vein thrombophlebitis)
Rare:	Pulmonary embolism, arterial thrombosis, cerebral infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough

Gastrointestinal disorders	
Common:	Nausea, dyspepsia[1], constipation, abdominal pain, diarrhoea, vomiting
Uncommon:	Dry mouth, stomatitis[1]
Hepatobiliary disorders	
Uncommon:	Increased hepatic enzymes, hyperbilirubinemia, jaundice
Not known:	Hepatitis
Skin and subcutaneous tissue disorders	
Very common:	Hyperhidrosis
Common:	Alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), dry skin
Uncommon:	Pruritus, urticaria
Not known:	Angioedema, toxic epidermal necrolysis, erythema multiforme
Angioedema, toxic epidermal necrolysis, erythema multiforme	
Very common:	Arthralgia
Common:	Myalgia, bone pain[1], osteoporosis, bone fractures, arthritis
Not known:	Trigger finger
Renal and urinary disorders	
Uncommon:	Pollakiuria
Reproductive system and breast disorders	
Common:	Vaginal haemorrhage
Uncommon:	Vaginal discharge, vulvovaginal dryness, breast pain
General disorders and administration site conditions	
Very common:	Fatigue (including asthenia, malaise)
Common:	Peripheral oedema, chest pain
Uncommon:	General oedema, mucosal dryness, thirst, pyrexia
Investigations	
Common:	Weight increased
Uncommon	Weight decreased

1 Adverse drug reactions may occur only in the metastatic setting

Overdose

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

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Endocrine therapy. Hormone antagonist and related agents: aromatase inhibitor, ATC code:L02BG04.

Pharmacodynamic properties

The elimination of oestrogen-mediated growth stimulation is a prerequisite for tumour response in cases where thegrowth of tumour tissue depends on the presence of oestrogens and endocrine therapy is used. In postmenopausalwomen, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens -primarily androstenedione and testosterone - to oestrone and oestradiol.

The suppression of oestrogen biosynthesis inperipheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

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

In healthy postmenopausal women, single doses of 0.1 mg, 0.5 mg, and 2.5 mg letrozole suppress serum oestrone andoestradiol by 75%, 78% and 78% from baseline respectively. Maximum suppression will be achieved in 48-78 hours.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg suppressed plasmaconcentration of oestradiol, oestrone, and oestrone sulphate by 75-95% from baseline in all patients treated. With dosesof 0.5 mg and higher, many values of oestrone and oestrone sulphate were below the limit of detection in the assays,indicating that higher oestrogen suppression will be achieved with these doses. Oestrogen suppression will be maintainedthroughout treatment in all these patients.

Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroid genesis has not been observed.No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxyprogesterone, and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose ofletrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 mg,0.25 mg, 0.5 mg, 1 mg, 2.5 mg, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus,glucocorticoid and mineralocorticoid supplementation is not necessary.

No changes will be noted in plasma concentrations of androgens (androstenedione and testosterone) among healthypostmenopausal women after 0.1 mg, 0.5 mg, and 2.5 mg single doses of letrozole or in plasma concentrations ofandrostenedione among postmenopausal patients treated with daily doses of 0.1 mg to 5 mg, indicating that theblockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH andFSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4, and T3 uptake test.

Pharmacokinetic properties

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Foodslightly decreases the rate of absorption (median t_{max} 1 hour fasted versus 2 hours fed; and mean C_{max} 129 ± 20.3nmol/litre fasted versus 98.7 ± 18.6 nmol/litre fed) but the extent of absorption (AUC) is not changed. The minor effect onthe

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 inerythrocytes is about 80% of that in plasma. After administration of 2.5 mg 14C-labelled letrozole, approximately 82% ofthe radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole israpidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 l/kg.

Biotransformation

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole(CLm = 2.1 l/h) but is relatively slow when compared to hepatic blood flow (about 90 l/h). The cytochrome P450isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minorunidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole.

Within 2 weeks after administration 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 urineup to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to twounidentified metabolites, and 6% to unchanged letrozole.

Elimination

The apparent terminal elimination half-life in plasma is about 2 to 4 days. After daily administration of 2.5 mg steadystatelevels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higherthan concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-statevalues predicted from the concentrations measured after a single dose, indicating a slight non-linearity in thepharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state levels are maintained over time, itcan be concluded that no continuous accumulation of letrozole occurs.

Special populations

Elderly

Age had no effect on the pharmacokinetics of letrozole.

Renal impairment

No dose adjustment is required for patients with renal impairment (CLcr ≥10 mL/min). Little information isavailable in patients with severe impairment of renal function (CLcr<10 mL/min).

Hepatic impairment

Letrozole should be administered with caution topatients with severe hepatic impairment and after consideration of the risk/benefit in the individual patient.

PHARMACEUTICAL PARTICULARS

List of excipients

Lactose monohydrate, Cellulose microcrystalline, Sodium starch glycolate (Type A), Maize starch, Silica colloidal anhydrous, Magnesium stearate, Opadry yellow and Purified Water.

Incompatibilities

Not applicable

Shelf life

24 months.

Special precautions for storage

Do not store above 30°C.Store in original pack and protect from light.

Nature and contents of container

Blister of (3x10's) tablets.

Manufactured by:

Eugia Pharma Specialities Limited,

Sy No. 550, 551 & 552, Kolthur (Village), Shamirpet (Mandal),

Medchal-Malkajgiri District, Telangana, India.

MARKETING AUTHORISATION HOLDER

AUROBINDO

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DATE OF PREPARATION OF THIS LEAFLET

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