LETARA

Letrazole 2.5 mg film-coated tablets

NAME OF THE MEDICINE

LETARA Active substance: 4,4'-[(1H-1,2,4-triazol-1-yl)-methylene] bis-benzonitrile (INN/USAN= letrozole).
Each film-coated tablet contains 2.5 mg letrazole.
For a full list of excipients, see List of excipients (Further information).

PRESENTATION

Letrozole 2.5 mg Tablets are yellow to dark yellow round, film coated, biconvex tablets, engraved with 'L' on one face and plain on the other. The tablets contain lactose (see List of excipients).

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

USES

Actions
Pharmacodynamic properties
Pharmacotherapeutic group: Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent (ATC code L02B G04).

Pharmacodynamic effects
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, 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). The suppression of oestrogen biosynthesis in peripheral 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 of the cytochrome P_{450} subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

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

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 to 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

Letrozole is highly 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 among postmenopausal patients treated with a daily dose of letrozole 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 were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1 mg, 0.5 mg and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 to 5 mg, 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 is thyroid function as evaluated by TSH, T4 and T3 uptake.

PHARMACOKINETICS

Absorption
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median tmax: 1 hour fasted versus 2 hours fed; and mean Cmax: 129 ± 20.3 nmol/L fasted versus 98.7 ± 18.6 nmol/L fed), 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 meal times.

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. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was 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 (CLm= 2.1 L/h), but is relatively slow when compared to hepatic blood flow (about 90L/h). The cytochrome P_{450} isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolities, 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 urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucoronide 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 had no effect on the pharmacokinetics of letrozole.

Indications
- 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.

DOSAGE AND ADMINISTRATION

LETARA should be administered once daily. Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

Adult and elderly patients
The recommended dose of LETARA is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with LETARA should continue for 5 years or until tumour relapse occurs, whichever comes first.
In patients with metastatic disease, treatment with LETARA should continue until tumour 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 mild hepatic impairment or renal impairment (creatinine clearance ≥ 30 mL/min.). Insufficient data are available to justify a dose advice in cases of renal insufficiency with a creatinine clearance less than 30 mL/min or in patients with severe hepatic insufficiency. Patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision (see Pharmacokinetics).

CONTRADICTIONS

Known hypersensitivity to the active substance or to any of the excipients. Premenopausal endocrine status; pregnancy, lactation (see Pregnancy and lactation).

WARNINGS AND PRECAUTIONS

Renal impairment
Letrozole has not been investigated in patients with creatinine clearance <10 mL/min nor in a sufficient number of patients with a creatinine clearance less than 30 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of Letrozole. As letrozole is weakly bound to plasma proteins (see Pharmacokinetics), it is anticipated that it could be removed from circulation by dialysis. Similar caution should be exercised in patients with severe hepatic insufficiency.

Hepatic impairment
In patients with severe hepatic cirrhosis 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 (see Adverse effects).

Pregnancy (Category D) and lactation
PregnancyLetrozole is contraindicated during pregnancy (see Contraindications).

Women of 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 (see Contraindications).

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.

ADVERSE EFFECTS

Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with oestrogen deprivation.

The most frequently reported adverse reactions in the clinical studies were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with Letrozole.

Table 1
Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common, common, uncommon, rare, very rare including isolated report.

Infections and infestations	
Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Tumour pain[6]
Blood and the lymphatic system disorders	
Uncommon	Leukopenia
Metabolism and nutrition disorders	
Common	Anorexia, appetite increase, hypercholesterolemia
Uncommon	General oedema
Psychiatric disorders	
Common	Depression
Uncommon	Anxiety[1]
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Somnolence, insomnia, memory impairment, dysaesthesia[2], taste disturbance, cerebrovascular accident
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Uncommon	Palpitations, tachycardia
Vascular disorders	
Uncommon	Thrombophlebitis[3], hypertension, ischemic cardiac events[7]
Rare	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough
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[4]
Uncommon	Pruritus, dry skin, urticaria
Very rare:	Angioedema, anaphylactic reaction
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Myalgia, bone pain, osteoporosis, bone fractures
Uncommon	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[5], peripheral oedema
Uncommon	Pyrexia, mucosal dryness, thirst
Investigations	
Common	Weight increase
Uncommon	Weight loss

1. including nervousness, irritability
2. including paraesthesia, hypoaesthesia
3. including superficial and deep thrombophlebitis
4. including erythematous, maculopapular, psoriaform and vesicular rash
5. including asthenia and malaise
6. in metastatic/neoadjuvant setting only

INTERACTIONS

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of letrozole with these drugs does not result in clinically significant drug interactions.

A review of the clinical trial database indicated no evidence of other clinically relevant interaction with other commonly prescribed drugs.

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

Letrozole inhibits in vitro the cytochrome P_{450}-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in drug 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 drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

OVERDOSAGE

Isolated cases of overdosage with Letrozole have been reported.

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

PHARMACEUTICAL PRECAUTIONS

Incompatibilities
Not applicable.

Shelf life
36 months

Special precautions for storage
Do not store above 30°C, protect from moisture.
LETARA should be kept out of the reach and sight of children.

Instructions for use/handling
No specific instructions for use/handling.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Carton of blisters containing 30 tablets.

List of Excipients
Colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hydroxypropyl methylcellulose, polyethylene glycol 8000, talc, titanium dioxide (E 171), iron oxide yellow (E 172).

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DATE OF PREPARATION

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304505

Description: Letara 2.5 mg TAB 304505
Size: 297 x 210 mm
Printed: Black
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