15-05-2023
4th Copy

(NEW LAUNCHING)

210mm

GRUDIZ® Tablet
(L e t r o z o l e)

QUALITATIVE AND QUANTITATIVE COMPOSITION

GRUDIZ® 2.5mg Tablet
Each film coated tablet contains:
Letrozole USP.....2.5mg

PHARMACEUTICAL FORM

Tablet.

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 induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.
- Neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where 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 2.5mg once daily. No dose adjustment is required for elderly patients.
  - In patients with advanced or metastatic breast cancer, treatment with letrozole should continue until tumor progression is evident.
  - In the adjuvant and extended adjuvant setting, treatment with letrozole should continue for 5 years or until tumor relapse occurs, whichever is first.
  - In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered.
- In the neoadjuvant setting, treatment with letrozole could be continued for 4 to 8 months in order to establish optimal tumor reduction.
  - If the response is not adequate, treatment with letrozole should be discontinued and surgery scheduled and/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 and adolescents aged up to 17 years have not been established. Limited data are available.
Renal impairment:
No dosage adjustment of letrozole is required for patients with renal insufficiency with creatinine clearance ≥10ml/min. Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 10ml/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.
Method of administration:
Letrozole should be taken orally and can be taken with or without food. The missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose (within 2 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 2.5mg recommended dose, over-proportionality in systemic exposure was observed.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance.
- Premenopausal endocrine status
- Pregnancy.
- Breast-feeding.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Menopausal status:
In patients whose menopausal status is unclear, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and/or oestradiol levels should be measured before initiating treatment with letrozole. Only women of postmenopausal endocrine status should receive letrozole.
Renal Impairment:
Letrozole has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10ml/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 approximately doubled 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 at increased risk of osteoporosis, should have their bone mineral density formally assessed prior to the commencement of adjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole. Treatment or prophylaxis 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 on the patient's safety profile.
Tendonitis and tendon rupture:
Tendonitis and tendon ruptures (rare) may occur. Close monitoring of the patients and appropriate measures (e.g. immobilization) must be initiated for the affected tendon.
Other warnings:
Co-administration of letrozole with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole. This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicinal product contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Interaction with Cimetidine:
Cimetidine, a weak, unspecific inhibitor of CYP450 enzymes, did not affect the plasma concentrations of letrozole. The effect of potent CYP450 inhibitors is unknown.
Interaction with tamoxifen, other anti-oestrogens or oestrogens:
Tamoxifen, other anti-oestrogens or oestrogen-containing therapies may diminish the pharmacological action of letrozole. In addition, co-administration of tamoxifen with letrozole has been shown to substantially decrease plasma concentrations of letrozole. Co-administration of letrozole with tamoxifen, other anti-oestrogens or oestrogens should be avoided.
Letrozole inhibits the cytochrome P450 isoenzymes 2A6 and 2C19:
Caution is indicated when giving letrozole concomitantly whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow (e.g. phenytoin, clopidogrel).

FERTILITY, PREGNANCY AND LACTATION:
Fertility:
The pharmacological action of letrozole 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.
Pregnancy:
Based on human experience in which there have been isolated cases of birth defects (labial fusion, ambiguous genitalia), letrozole may cause congenital malformations when administered during pregnancy. 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 be excluded. Letrozole is contraindicated during breast-feeding.
Women of Perimenopausal status or child-bearing potential:
Letrozole should only be used in women with a clearly established post-menopausal status. As there are reports of women regaining ovarian function during treatment with letrozole despite a clear postmenopausal status at start of therapy, the physician needs to discuss adequate contraception when necessary.

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EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Letrozole has minor influence on the 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.

UNDESIRABLE EFFECTS:
- **Infections and infestations:** ***Uncommon:*** Urinary tract infection.
- **Neoplasms, Benign, malignant and unspecified (including cysts and polyps):** ***Uncommon:*** Tumor pain.
- **Blood and lymphatic system disorders:** ***Uncommon:*** Leukopenia.
- **Immune system disorders:** ***Not known:*** Anaphylactic reactions.
- **Metabolism and nutrition disorders:** ***Very common:*** Hypercholesterolemia. ***Common:*** Anorexia, appetite increase.
- **Psychiatric disorders:** ***Common:*** Depression. ***Uncommon:*** Anxiety (including nervousness), irritability.
- **Nervous system disorders:** ***Common:*** Headache, dizziness. ***Uncommon:*** Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), taste disturbance, cerebrovascular accident, carpal tunnel syndrome.
- **Eye disorders:** ***Uncommon:*** Cataract, eye irritation, blurred vision.
- **Cardiac disorders:** ***Common:*** Palpitations. ***Uncommon:*** Tachycardia, ischemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia).
- **Vascular disorders:** ***Very Common:*** Hot flushes. ***Common:*** Hypertension. ***Uncommon:*** Thrombophlebitis (including superficial and deep vein thrombophlebitis). ***Rare:*** Pulmonary embolism, arterial thrombosis, cerebrovascular infarction.
- **Respiratory, thoracic and mediastinal disorders:** ***Uncommon:*** Dyspnoea, cough.
- **Gastrointestinal disorders:** ***Common:*** Nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain. ***Uncommon:*** Stomatitis, dry mouth.
- **Hepatobiliary disorders:** ***Uncommon:*** Increased hepatic enzymes, hyperbilirubinemia, jaundice. ***Not Known:*** Hepatitis.
- **Skin and subcutaneous tissue disorders:** ***Very Common:*** Increased sweating. ***Common:*** Alopecia, rash (including erythematous, maculopapular, psoriaform and vesicular rash), dry skin. ***Uncommon:*** Pruritus, urticaria. ***Not known:*** Angioedema, toxic epidermal necrolysis, erythema multiforme.
- **Musculoskeletal and connective tissue disorders:** ***Very Common:*** Arthralgia. ***Common:*** Myalgia, bone pain, osteoporosis, bone fractures, arthritis. ***Uncommon:*** Tendonitis. ***Rare:*** Tendon rupture. ***Not known:*** Trigger finger.
- **Renal and urinary disorders:** ***Uncommon:*** Increased urinary frequency.
- **Reproductive system and breast disorders:** ***Common:*** Vaginal bleeding. ***Uncommon:*** Vaginal discharge, vaginal dryness, breast pain.
- **General disorders and administration site conditions:** ***Very Common:*** Fatigue (including asthenia, malaise). ***Common:*** Peripheral oedema, chest pain. ***Uncommon:*** General oedema, pyrexia, mucosal dryness, thirst.
- **Investigations:** ***Common:*** Weight increase. ***Uncommon:*** Weight loss.

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

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group:
Endocrine therapy. Hormone antagonist and related agents: Aromatase inhibitor. **ATC code:** L02B G04.
Mechanism of action:
The elimination of oestrogen-mediated growth stimulation is a prerequisite for tumor response in cases where the growth of tumor tissue depends on the presence of oestrogen and endocrine therapy is used. In postmenopausal women, oestrogen 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 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 aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present.

PHARMAKOKINETIC PROPERTIES:
Absorption:
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max}: 1 hour fasted versus 2 hours fed; and mean C_{max}: 129 ± 20.3nmol/L fasted versus 98.7 ± 18.6nmol/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 mealtimes.
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 2.5mg 14C-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 ± 0.47L/kg.
Biotransformation:
Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CLm= 2.1L/h) but is relatively slow when compared to hepatic blood flow (about 90L/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.
Elimination:
The apparent terminal elimination half-life in plasma is about 2 to 4 days. After daily administration of 2.5mg 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 2.5mg, 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 2.5mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.
Linearity/non-linearity:
The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10mg (dose range: 0.01 to 30mg) and after daily doses up to 1.0mg (dose range: 0.1 to 5mg). After a 30mg single oral dose there was a slightly dose over-proportional increase in AUC value. The dose over-proportionality is likely to be the result of a saturation of metabolic elimination processes. Steady levels were reached after 1 to 2 months at all dosage regimens tested (0.1-5.0mg daily).
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 ≥10mL/min). Little information is available in patients with severe impairment of renal function (CLcr <10mL/min).
Hepatic impairment:
Letrozole should be administered with caution to patients with severe hepatic impairment and after consideration of the risk/benefit in the individual patient.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
GRUDIZ® 2.5mg tablet in a pack of 10's.

INSTRUCTIONS
Dosage: As directed by the physician.
To be sold on prescription of a registered medical practitioner only.
Keep out of the reach of children.
Do not store over 30°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.

گروڈز® ٹیبلٹ
(لیٹروزول)

ہدایات:
خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،
گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔

Manufactured by:
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