Danletro 2.5mg

(L e t r o z o l e) Tablets U.S.P.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Danletro 2.5mg Tablets U.S.P.

Each film-coated tablet contains:

Letrozole U.S.P. 2.5mg

DESCRIPTION

Danletro tablets for oral administration contains 2.5mg of letrozole, a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water.

CLINICAL PHARMACOLOGY

Mechanism of Action: Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system; it inhibits the conversion of androgens to estrogens. In adult nontumor- and tumor-bearing female animals, letrozole is as effective as ovariectomy in reducing uterine weight, elevating serum LH, and causing the regression of estrogen-dependent tumors. In contrast to ovariectomy, treatment with letrozole does not lead to an increase in serum FSH. Letrozole selectively inhibits gonadal steroidogenesis but has no significant effect on adrenal mineralocorticoid or glucocorticoid synthesis.

Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. Treatment of women with letrozole significantly lowers serum estrone, estradiol and estrone sulfate and has not been shown to significantly affect adrenal corticosteroid synthesis, aldosterone synthesis, or synthesis of thyroid hormones. **Pharmacodynamics:** In postmenopausal patients with advanced breast cancer, daily doses of 0.1mg to 5mg Danletro (letrozole) suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75% to 95% from baseline with maximal suppression achieved within two three days. Suppression is dose related, with doses of 0.5mg and higher giving many values of estrone and estrone sulfate that were below the limit of detection in the assays. Estrogen suppression was maintained throughout treatment in all patients treated at 0.5mg or higher. Letrozole is highly specific in inhibiting aromatase activity. There is no impairment of adrenal steroidogenesis. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17 hydroxy-progesterone, ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of Letrozole 0.1mg to 5mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5mg did not indicate any attenuation of aldosterone or cortisol production. Glucocorticoid or mineralocorticoid supplementation is, therefore, not necessary. No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5mg single doses of Letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1mg to 5mg. This indicates that the blockade of estrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH were not affected by letrozole in patients, nor was thyroid function as evaluated by TSH levels, T3 uptake, and T4 levels. **Pharmacokinetics: Absorption and Distribution:** Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled letrozole is recovered in urine. Letrozole's terminal elimination half life is about 2 days and steady state plasma concentration after daily 2.5mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than 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. These steady state levels are maintained over extended periods, however, and continuous accumulation of letrozole does not occur. Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg). **Metabolism and Excretion:** Metabolism to a pharmacologically inactive carbinol metabolite (4,4' methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. Of the radiolabel recovered in urine, at least 75%was the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and 6% was unchanged letrozole. In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. In human liver microsomes, letrozole inhibited CYP2A6 and CYP2C19, however, the clinical significance of these findings is unknown.

INDICATIONS AND USAGE

- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Adjuvant treatment of oestrogen receptor positive invasive early breast cancer in postmenopausal women.
- Advanced breast cancer in postmenopausal women (naturally or artificially induced menopause) in whom other antiestrogen therapy has failed.
- Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received standard adjuvant tamoxifen therapy for 5 years.
- Neo adjuvant treatment in postmenopausal women with localized hormone receptor positive, human epidermal growth factor-2 negative breast cancer where chemotherapy is not suitable and surgery not yet indicated.

CONTRAINDICATIONS

Known hypersensitivity to the active substance, or to any of the excipients. Not indicated for premenopausal women.

Letrozole is contraindicated during breast-feeding. Letrozole is contraindicated during pregnancy. Letrozole can cause fetal harm.

INTERACTIONS

Tamoxifen: Coadministration of Lets and tamoxifen 20mg daily resulted in a reduction of letrozole plasma levels of 38% on average. Clinical experience in the second-line breast cancer trials (AR/BC2 and AR/BC3) indicates that the therapeutic effect of Letrozole therapy is not impaired if Letrozole is administered immediately after tamoxifen. **Cimetidine:** A pharmacokinetic interaction study with cimetidine showed no clinically significant effect on letrozole pharmacokinetics. **Warfarin:** An interaction study with warfarin showed no clinically significant effect of letrozole on warfarin pharmacokinetics. Other anticancer agents There is no clinical experience to date on the use of Letrozole in combination with other anticancer agents.

USE IN SPECIFIC POPULATION

Pregnancy: Category X: Danletro can cause fetal harm and is contraindicated for use in pregnant women. In post-marketing reports, use of letrozole during pregnancy resulted in cases of spontaneous abortions and congenital birth defects. Fetal anomalies included incomplete ossification of the skull, sternebrae, and fore and hind legs. Danletro is contraindicated during pregnancy. **Nursing Mothers:** It is not known if letrozole is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from letrozole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **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. **Pediatric Use:** The safety and effectiveness in pediatric patients have not been established. The safety and efficacy of Danletro in children and adolescents aged up to 17 years have not been established.

Geriatric Use:

Adult and elderly patients:

- The recommended dose of Danletro is 2.5mg once daily. No dose adjustment is required for elderly patients.
- In patients with advanced or metastatic breast cancer, treatment with Danletro should continue until tumour progression is evident.
- In the adjuvant and extended adjuvant setting, treatment with Letrozole should continue for 5 years or until tumour 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 Danletro could be continued for 4 to 8 months in order to establish optimal tumour reduction. If the response is not adequate, treatment with Danletro should be discontinued and surgery scheduled and/or further treatment options discussed with the patient.

Renal impairment: No dosage adjustment of Danletro is required for patients with renal insufficiency with creatinine clearance ≥10 ml/min. Caution is there if creatinine clearance less than 10ml/minute. **Hepatic impairment:** No dosage adjustment is recommended for patients with mild to moderate hepatic impairment, although Danletro blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis. The dose of Danletro in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose of Danletro for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on Danletroexposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined. Caution should be there in sever impairment.

PRECAUTIONS

Bone Effects: Use of Danletro may cause decreases in bone mineral density (BMD). Danletro 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. **Cholesterol:** Consideration should be given to monitoring serum cholesterol. **Hepatic Impairment:** Subjects with cirrhosis and severe hepatic impairment who were dosed with 2.5 mg of Danletro experienced approximately twice the exposure to Danletro as healthy volunteers with normal liver function. Therefore, a dose reduction is recommended for this patient population. **Fatigue and Dizziness:** Because fatigue, dizziness, and somnolence have been reported with the use of Danletro, caution is advised when driving or using machinery until it is known how the patient reacts to Danletro use. **Laboratory Test Abnormalities:** Moderate decreases in lymphocyte counts, of uncertain clinical significance, were observed in some patients receiving Danletro 2.5mg. This depression was transient in about half of those affected. Two patients on Danletro developed thrombocytopenia; relationship to the study drug was unclear. Patient withdrawal due to laboratory abnormalities, whether related to study treatment or not, was infrequent. **Embryo-Fetal Toxicity:** Based on post-marketing reports, findings from animal studies and the mechanism of action, Danletro can cause fetal harm and is contraindicated for use in pregnant women. **Co-administration of Danletro with tamoxifen:** Co-administration of Danletro with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole. **Galactose intolerant patients:** As the tablets contain lactose, Danletro is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption. **Menopausal status:** In patients whose menopausal status is unclear, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or oestradiol levels should be measured before initiating treatment with Brand Name. Only women of postmenopausal endocrine status should receive Danletro. **Avoid driving and using machines:** Since fatigue and dizziness have been observed with the use of Danletro and somnolence has been reported uncommonly, caution is advised when driving or using machines.

ADVERSE REACTIONS

Common or very common: Abdominal pain ,alopecia ,anorexia,appetite increase, arthralgia,bone fracture, Constipation, depression, diarrhea, dizziness, dry skin, dyspepsia, fatigue, headache, hot flushes, hypercholesterolaemia, hypertension, increased sweating, musculoskeletal pain, nausea, osteoporosis, peripheral oedema, rash, vaginal bleeding,vomiting, weight changes. **Uncommon:** Anxiety, arthritis, blurred vision, breast pain, cardiac events, cataract, cerebrovascular events, cough, Dysaesthesia, dyspnea, eye irritation, general oedema, insomnia, leucopenia, memory impairment, mucosal Dryness, palpitation, pruritus, pyrexia, stomatitis, tachycardia, taste disturbance, thrombophlebitis, tumour pain, urinary frequency, urinary-tract infection, urticaria. vaginal discharge. **Rare:** Arterial thrombosis . pulmonary embolism. **Frequency not known:** Hepatitis ,toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

The recommended dose of Danletro is one 2.5 mg tablet administered once a day, without regard to meals. **Use in Adjuvant Treatment of Early Breast Cancer:** In the adjuvant setting, the optimal duration of treatment with letrozole is unknown. In both the adjuvant study and the postapproval adjuvant study, median treatment duration was 5 years. Treatment should be discontinued at relapse. **Use in Extended Adjuvant Treatment of Early Breast Cancer:** In the extended adjuvant setting, the optimal treatment duration with Letrozole is not known. The planned duration of treatment in the study was 5 years. In the final updated analysis, conducted at a median follow-up of 62 months, the median treatment duration for Lets was 60 months. Seventy-one (71%) percent of patients were treated for at least 3 years and 58% of patients completed at least 4.5 years of extended adjuvant treatment. The treatment should be discontinued at tumor relapse. **Use in First and Second Line Treatment of Advanced Breast Cancer:** In patients with advanced disease, treatment with Letrozole should continue until tumor progression is evident. **Overdosage:** Isolated cases of overdose with Letrozole have been reported. No specific treatment for overdose is known; treatment should be symptomatic and supportive.

INSTRUCTIONS

Dosage as directed by the physician.

Store below 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of children.

PRESENTATION

Danletro (Letrozole) 2.5mg tablets U.S.P. are available in Alu-Alu blister pack of 10's with leaflet.

Manufactured for:

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