Lerozol®

Letrozole

COMPOSITION

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

MECHANISM OF ACTION

Letrozole is a nonsteroidal aromatase inhibitor. It inhibits the conversion of androgen to estrogen. 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 the adrenal corticosteroid synthesis, ldosterone synthesis, or synthesis of thyroid hormones.

PHARMACOKINETICS

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 2.5 mg 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 2.5 mg. 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 strongly inhibited CYP2A6 and moderately inhibited CYP2C19.

PHARMACODYNAMICS

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg Lerozol suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75%-95% from baseline with maximal suppression achieved within two-three days. Suppression is dose-related, with doses of 0.5 mg 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 0.5 mg 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 0.1 mg to 5 mg. 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 5 mg did not indicate any attenuation of aldosterone or cortisol production. No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5 mg single doses or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 mg to 5 mg. 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.

INDICATION

- 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 5 years of adjuvant tamoxifen therapy.
- First-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.
- Treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

DOSAGE AND ADMINISTRATION

The recommended dose is one 2.5 mg tablet administered once a day, regardless to meals. In patients with advanced disease, treatment with **Lerozol®** Tablet should be continued until tumor progression is evident.

Treatment should be discontinued at tumor relapse.

No dose adjustment is required for elderly patients. Patients treated with **Lerozol®** Tablet do not require glucocorticoid or mineralocorticoid replacement therapy.

Renal Impairment

No dosage adjustment is required for patients with renal impairment if creatinine clearance is 10 ml / min.

Hepatic Impairment

No dosage adjustment is recommended for patients with mild to moderate hepatic impairment. The dose of **Lerozol®** in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on **Lerozol®** exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

CONTRAINDICATION

Lerozol® Tablet is contraindicated in patients with known hypersensitivity to Letrozole or any of its excipients.

DRUG INTERACTION

A pharmacokinetic interaction study with cimetidine showed no clinically significant effect on Letrozole pharmacokinetics. An interaction study with warfarin showed no clinically significant effect of Letrozole on warfarin pharmacokinetics. In in-vitro experiments, Letrozole showed no significant inhibition in the metabolism of diazepam. Similarly, no significant inhibition of Letrozole metabolism by diazepam was observed. Coadministration of Letrozole and tamoxifen 20 mg daily resulted in a reduction of Letrozole plasma levels of 38% on average. Clinical experience in the second-line breast cancer pivotal trials indicates that the therapeutic effect of Letrozole therapy is not impaired if Letrozole is administered immediately after tamoxifen.

PRECAUTION

Since fatigue and dizziness have been observed with the use of Letrozole and somnolence was uncommonly reported, caution is advised when driving or using machinery.

Pregnancy

Pregnancy Category D.

Nursing Mothers
It is not known if Letrozole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Letrozole is administered to a nursing woman.

Pediatric Use
The safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTION
Lerozol® Tablet (Letrozole) is generally well tolerated. The observed adverse reactions are mild or moderate in nature including Hot Flashes, Night Sweats, Weight Increase, Nausea, Vaginal Bleeding & Irritation, Endometrial Proliferation Disorders etc.

STORAGE CONDITION
Store in a cool and dry place protected from light and moisture.

HOW SUPPLIED
Lerozol® Tablet: Box containing 1x5 tablets in blister pack.