# Letrozol

Letrozole USP 2.5mg Tablet

DRUG INTERNATIONAL LTD.

## COMPOSITION

**Letrozol Tablet :** Each film coated tablet contains Letrozole USP 2.5mg.

## CLINICAL PHARMACOLOGY

### Mechanism of Action:

The growth of some cancers of the breast is stimulated or maintained by estrogens. Treatment of breast cancer thought to be hormonally responsive (i.e., estrogen and/or progesterone receptor positive or receptor unknown) has included a variety of efforts to decrease estrogen levels (ovariectomy, adrenalectomy, hypophysectomy) or inhibit estrogen effects (antiestrogens and progestational agents). These interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

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.

### 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

**Adjuvant Treatment of Early Breast Cancer:** It is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

**Extended Adjuvant Treatment of Early Breast Cancer:** It is indicated for the extended adjuvant treatment of early breast cancer in postmenopausal women, who have received 5 years of adjuvant Tamoxifen therapy. The effectiveness of Letrozole in extended adjuvant treatment of early breast cancer is based on an analysis of disease-free survival in patients treated with Letrozole for a median of 60 months.

**First and Second-Line Treatment of Advanced Breast Cancer:** It is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Letrozole is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

## DOSAGE AND ADMINISTRATION

The recommended dose of Letrozole is one 2.5mg 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 Letrozole 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.

**Use in Hepatic Impairment:** No dosage adjustment is recommended for patients with mild to moderate hepatic impairment, although Letrozole blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis. The dose of Letrozole in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose of Letrozole for such patients is 2.5mg administered every other day. The effect of hepatic impairment on Letrozole exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

**Use in Renal Impairment:** No dosage adjustment is required for patients with renal impairment if creatinine clearance is greater than or equal to 10 ml/min. Or, as directed by the registered physician.

## ADVERSE EFFECTS

The following adverse reactions from the use of Letrozole are bone effects, increases in cholesterol, fatigue and dizziness.

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

## CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to Letrozole or to any component of the formulation. It can cause fetal harm.

## DRUG INTERACTIONS

### Tamoxifen

Coadministration of Letrozole 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 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.

## PRECAUTIONS

### Bone Effects:

Use of Letrozole may cause decreases in bone mineral density (BMD). Consideration should be given to monitoring BMD. Results of a safety study to evaluate safety in the adjuvant setting comparing the effect on lumbar spine (L2-L4) BMD of adjuvant treatment with Letrozole to that with Tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the Letrozole arm compared to a median increase of 0.3% in the Tamoxifen arm (difference = 4.4%) ($P<0.0001$). Updated results from the BMD substudy in the extended adjuvant setting demonstrated that at 2 years patients receiving Letrozole had a median decrease from baseline of 3.8% in hip BMD compared to a median decrease of 2.0% in the placebo group. The changes from baseline in lumbar spine BMD in Letrozole and placebo treated groups were not significantly different.

In the adjuvant trial the incidence of bone fractures at any time after randomization was 14.7% for Letrozole and 11.4% for Tamoxifen at a median follow-up of 96 months. The incidence of osteoporosis was 5.1% for Letrozole and 2.7% for Tamoxifen. In the extended adjuvant trial the incidence of bone fractures at any time after randomization was 13.3% for Letrozole and 7.8% for placebo at a median follow-up of 62 months. The incidence of new osteoporosis was 14.5% for Letrozole and 7.8% for placebo.

### Cholesterol:

Consideration should be given to monitoring serum cholesterol. In the adjuvant trial, hypercholesterolemia was reported in 52.3% of Letrozole patients and 28.6% of Tamoxifen patients. Grade 3-4 hypercholesterolemia was reported in 0.4% of Letrozole patients and 0.1% of Tamoxifen patients. Also in the adjuvant setting, an increase of greater than or equal to 1.5 x upper limit of normal (ULN) in total cholesterol (generally nonfasting) was observed in patients on monotherapy who had baseline total serum cholesterol within the normal range (i.e., less than =1.5 x ULN) in 155/1843 (8.4%) patients on Letrozole vs 71/1840 (3.9%) patients on Tamoxifen. Lipid lowering medications were required for 29% of patients on Letrozole and 20% on Tamoxifen.

### Hepatic Impairment:

Subjects with cirrhosis and severe hepatic impairment who were dosed with 2.5mg of Letrozole experienced approximately twice the exposure to Letrozole as healthy volunteers with normal liver function. Therefore, a dose reduction is recommended for this patient population. The effect of hepatic impairment on Letrozole exposure in cancer patients with elevated bilirubin levels has not been determined.

### Fatigue and Dizziness:

Because fatigue, dizziness, and somnolence have been reported with the use of Letrozole, caution is advised when driving or using machinery until it is known how the patient reacts to Letrozole use.

### Pediatric Use:

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

### Use in Pregnancy:

Letrozole can cause fetal harm and is contraindicated for use in pregnant women.

### Use in Lactation:

It is not known if Letrozole is present in human milk. Because of the potential for serious adverse reactions in breastfed infants from Letrozole, lactating women should be advised not to breastfeed while taking Letrozole and for at least 3 weeks after the last dose.

## OVERDOSE

Isolated cases of Letrozole overdose have been reported. However, emesis could be induced if the patient is alert. In general, supportive care and frequent monitoring of vital signs are also appropriate.

## PHARMACEUTICAL INFORMATION

## STORAGE

Store below 30 $^{\circ}$C in a dry place. Protect from light. Keep out of the reach of children.

## PACKING

**Letrozol:** Each box contains 10 tablets in Alu-Alu blister pack.