Lexel

Letrozole 2.5 mg

COMPOSITION

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

DESCRIPTION

Letrozole is a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). It is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31, empirical formula $C_{17}H_{11}N_5$, and a melting range of 184°C-185°C.

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.

INDICATIONS

Adjuvant Treatment of Early Breast Cancer

Lexel is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Extended Adjuvant Treatment of Early Breast Cancer

Letrozole 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

Lexel 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.

For ovulation induction in anovulatory infertility like Polycystic Ovary Syndrome (PCOS)

Endometriosis

DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended dose of Lexel is one 2.5 mg tablet administered once a day, without regard to meals.

For ovulation induction in anovulatory infertility like Polycystic Ovary Syndrome (PCOS):
2.5 mg twice daily from day 3 to day 7 of cycle. Treatment should be continued at least for three cycles.

Endometriosis:
Letrozole 2.5 mg daily for 6 months

Use in Adjuvant Treatment of Early Breast Cancer

In the adjuvant setting, the optimal duration of treatment with Letrozole is unknown. The planned duration of treatment in the study was 5 years with 73% of the patients having completed adjuvant therapy. 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 was 60 months. Seventy-one percent of patients were treated for at least 3 years and 58% of patients completed 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 Lexel 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 2.5 mg 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 ≥10 mL/min.

CONTRAINDICATIONS

Letrozole may cause fetal harm when administered to a pregnant woman and the clinical benefit to premenopausal women with breast cancer has not been demonstrated. Letrozole is contraindicated in women who are or may become pregnant. If Letrozole is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

PRECAUTIONS

Bone Effects

Use of Letrozole may cause decreases in bone mineral density (BMD). Consideration should be given to monitoring BMD. Results of a substudy to evaluate safety in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (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 sub-study 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 13.8% for Letrozole and 10.5% for Tamoxifen. 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. 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. CTC grade 3-4 hypercholesterolemia was reported in 0.4% of Tetrozole patients and 0.1% of Tamoxifen patients. Also in the adjuvant setting, an increase of ≥1.5 X ULN in total cholesterol (generally non-fasting) was observed in patients on monotherapy who had baseline total serum cholesterol within the normal range (i.e., <=1.5 X ULN) in 151/1843 (8.2%) on Letrozole vs 57/1840 (3.2%). Lipid lowering medications were required for 25% of patients on Letrozole and 16% on Tamoxifen.

Hepatic Impairment

Subjects with cirrhosis and severe hepatic impairment who were dosed with 2.5 mg 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.

Laboratory Test Abnormalities

No dose-related effect of Letrozole on any hematologic or clinical chemistry parameter was evident. Moderate decreases in lymphocyte counts, of uncertain clinical significance, were observed in some patients receiving Letrozole 2.5 mg. This depression was transient in about half of those affected. Two patients on Letrozole developed thrombocytopenia; relationship to the study drug was unclear. Patient withdrawal due to laboratory abnormalities, whether related to study treatment or not, was infrequent.

ADVERSE EFFECTS

The most serious adverse reactions from the use of Letrozole are:

- Bone effects
- Increases in cholesterol

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.

DRUG INTERACTIONS

Tamoxifen

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 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.

PHARMACEUTICAL INFORMATION

Storage condition

Store in a cool and dry place, away from light. Keep out of the reach of children.

Packaging

Lexel Tablet: Each commercial box contains 1x10 tablets or 3x10 tablets in Alu-Alu blister pack.

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BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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