140mm

210mm

TABLET

Femol

(Letrozole USP)

فیمول ٹیبلٹ

(لیٹروزول۔ یو ایس پی)

COMPOSITION

Each tablet contains:

Letrozole (USP).....2.5mg

Product complies USP specs.

DESCRIPTION

Femol (letrozole) is a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). It is used in the treatment of hormonally-responsive breast cancer after surgery.

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.

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-estrogens.

• 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.

DOSAGE & ADMINISTRATION

Adult and elderly patients

•The recommended dose of letrozole tablets is 2.5 mg once daily. No dose adjustment is required for elderly patients.

•In patients with advanced or metastatic breast cancer, treatment with letrozole tablets should continue until tumor progression is evident.

•In the adjuvant and extended adjuvant setting, treatment with letrozole tablets 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 neo-adjuvant setting, treatment with Letrozole tablet could be continued for 4 to 8 months in order to establish optimal tumor reduction. If the response is not adequate, treatment with letrozole tablet should be discontinued and surgery scheduled and/or further treatment options discussed with the patient.

Pediatric population

Letrozole tablet is not recommended for use in children and adolescents. The safety and efficacy of Letrozole tablet in children and adolescents aged up to 17 years have not been established. Limited data are available and no recommendation on a posology can be made.

Renal Impairment

No dosage adjustment of Letrozole tablet is required for patients with renal insufficiency with creatinine clearance ⩾ 10 ml/min. Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 10 ml/min.

Hepatic impairment

No dose adjustment of Letrozole tablet 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. Patients with severe hepatic impairment (Child-Pugh C) require close supervision.

PHARMACODYNAMICS

In postmenopausal patients with advanced breast cancer, daily doses of 0.1mg to 5mg. Femol 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 orin plasma renin activity among postmenopausal patients treated with a daily dose of Femol 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. 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 2.5 mg single doses of Femol 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.

PHARMACOKINETICS

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median tmax 1 hour fasted versus 2 hours fed; and mean Cmax 129 ± 20.3 nmol/litre fasted versus 98.7 ± 18.6 nmol/litre 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 2.5 mg 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 = 2.1 L/h) but is relatively slow when compared to hepatic blood flow (about 90 L/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. Within 2 weeks after administration of 2.5 mg 14C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

Elimination

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2.5 mg 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 2.5 mg, 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 2.5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Linearity/nonlinearity

The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg (dose range: 0.01 to 30mg) and after daily doses up to 1.0 mg (dose range: 0.1 to 5mg). After a 30 mg 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).

WARNINGS AND PRECAUTIONS

Menopausal status

In patients whose menopausal status is unclear, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and/or estradiol levels should be measured before initiating treatment with Letrozole tablet. Only women of postmenopausal endocrine status should receive Letrozole tablet.

Renal impairment

Letrozole Tablets has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 ml/min. The potential risk/benefit to such patients should be carefully considered before administration of Letrozole.

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Linearity/nonlinearity

The pharmacokinetics of letrozole were dose proportional after single oral doses up

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ دھوپ، گرمی، نمی سے محفوظ اور بچوں کی پہنچ سے دور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.

From: Al-Sheikh Gulf Printers Tel: 35113411