Retzole®
(Letrozole USP)

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COMPOSITION
Each film coated tablet contains:
Letrozole USP..... 2.5mg
(USP Specification)

DESCRIPTION
Retzole tablets for oral administration contains 2.5 mg of Letrozole, a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). It is chemically described as 4, 4'-(1H-1,2,4-Triazol-1-ylmethylene) dibenzonitrile.

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 0.1 mg to 5 mg 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 0.5 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.

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 meal times.

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 ± 0.47 L/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. in vitro, but their individual contributions to Letrozole clearance in vivo have not been established. In an interaction study co-administration with cimetidine, which is known to inhibit only the 3A4 isoenzyme, did not result in a decrease in Letrozole clearance suggesting that in vivo the 2A6 isoenzyme plays an important part in total clearance. In this study a slight decrease in AUC and increase in Cmax were observed. 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 to 4 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.

INDICATIONS

• Adjuvant Treatment of Early Breast Cancer
Letrozole 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
Letrozole is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. It is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

DOSAGE AND ADMINISTRATION

• Recommended Dose
The recommended dose of Letrozole is one 2.5 mg tablet administered once a day, without regard to meals.

• 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 post approval adjuvant study, median treatment duration was 5 years. Treatment should be discontinued at relapse.

• 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

• First and Second-Line Treatment of Advanced Breast Cancer
In patients with advanced disease, treatment with Letrozole should continue until tumor progression is evident.

Dosage adjustment in special populations

Renal impairment
No dosage adjustment is required for patients with renal impairment if creatinine clearance is greater than or equal to 10 mL/min.

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.

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

Method of administration
Letrozole tablets should be taken orally and can be taken with or without food.
A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose (within 2 or 3 hours), the missed dose should be skipped, and the patient should go back to her regular dosage schedule. Doses should not be doubled because with daily doses over the 2.5 mg recommended dose, over-proportionality in systemic exposure was observed.

CONTRAINDICATIONS
• Hypersensitivity to the active substance or to any of the excipients.
• Premenopausal endocrine status
• Premenopausal, pregnant or lactating women

WARNING AND PRECAUTIONS

Bone effects
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. In the adjuvant setting a sequential treatment schedule (Letrozole 2 years followed by tamoxifen 3 years) could also be considered depending on the patient`s safety profile
As Letrozole is a potent oestrogen lowering agent, reductions in bone mineral density can be anticipated. During adjuvant treatment with Letrozole, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and patients treated with Letrozole tablets should be carefully monitored.

Cholesterol
Consideration should be given to monitoring serum cholesterol. In the adjuvant trial (BIG 1-98), 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 2.5 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.

Embryo-Fetal Toxicity
Based on post-marketing reports, findings from animal studies and the mechanism of action, Letrozole 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. Letrozole caused

embryo-fetal toxicities in rats and rabbits at maternal exposures that were below the maximum recommended human dose (MHRD) on a mg/m^2 basis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during therapy with Letrozole and for at least 3 weeks after the last dose.

ADVERSE REACTIONS
Infections and infestations
Uncommon: Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Tumour pain
Blood and lymphatic system disorders
Uncommon: Leucopenia
Immune system disorders
Very rare: Angioedema
Unknown: Anaphylactic reactions
Metabolism and nutrition disorders
Very common: Hypercholesterolaemia
Common: Anorexia, appetite increase.
Uncommon: General oedema
Psychiatric disorders
Common: Depression
Uncommon: Anxiety, irritability
Nervous system disorders
Common: Headache, dizziness
Uncommon: Somnolence, insomnia, memory impairment, dysesthesia, taste disturbance, Cerebrovascular accident, carpal tunnel syndrome.
Eye disorders
Uncommon: Cataract, eye irritation, blurred vision
Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia, ischaemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia)
Vascular disorders
Very common: Hot flushes
Common: Hypertension
Uncommon: Thrombophlebitis, ischemic cardiac events
Rare: Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough
Gastrointestinal disorders
Common: Nausea, dyspepsia, constipation, abdominal pain, diarrhoea, vomiting
Uncommon: Dry mouth, stomatitis
Hepatobiliary disorders
Uncommon: Increased hepatic enzymes, hyperbilirubinemia, jaundice.
Not known: Hepatitis
Skin and subcutaneous tissue disorders
Very common: Increased sweating
Common: Alopecia, rash, dry skin
Uncommon: Pruritus, urticarial
Not known: Toxic epidermal necrolysis, erythema multiforme.
Musculoskeletal and connective tissue disorders
Very common: Arthralgia
Common: Myalgia, bone pain, osteoporosis, bone fractures, arthritis
Uncommon: Tendonitis
Rare: Tendon rupture
Not Known: Trigger finger
Renal and urinary disorders
Uncommon: Increased urinary frequency
Reproductive system and breast disorders
Common: Vaginal bleeding
Uncommon: Vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions
Very common: Fatigue, hot flushes
Common: Peripheral oedema, chest pain.
Uncommon: General oedema, pyrexia, mucosal dryness, thirst
Investigations
Common: Weight increase
Uncommon: Weight loss

DRUG INTERACTIONS

Tamoxifen
Coadministration of Letrozole and tamoxifen 20 mg daily resulted in a reduction of Letrozole plasma levels of 38% on average (study P015). 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 (study P004) showed no clinically significant effect on Letrozole pharmacokinetics.

Warfarin
An interaction study (P017) 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 SPECIAL POPULATIONS

Women of perimenopausal status or child-bearing potential
Letrozole should only be used in women with a clearly established postmenopausal status. As there are reports of women regaining ovarian function during treatment with Letrozole despite a clear postmenopausal status at start of therapy, the physician needs to discuss adequate contraception when necessary.

Pregnancy
Letrozole is contraindicated during pregnancy.
Based on human experience in which there have been isolated cases of birth defects (labial fusion, ambiguous genitalia), Letrozole may cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity.

Lactation
Letrozole is contraindicated during breast-feeding. It is unknown whether Letrozole and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Fertility
The pharmacological action of Letrozole is to reduce oestrogen production by aromatase inhibition. In premenopausal women, the inhibition of oestrogen synthesis leads to feedback increases in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular growth, and can induce ovulation.

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

OVER DOSAGE
There is no clinical experience of overdosage only isolated cases of overdose with Letrozole have been reported. In animal studies, Letrozole exhibits only a slight degree of acute toxicity. In clinical trials, the highest single and multiple dose tested in healthy volunteers was 30 mg and 5 mg, respectively, the latter also being the highest dose tested in postmenopausal breast cancer patients. Each of these doses was well tolerated. There is no clinical evidence for a particular dose of Letrozole resulting in life-threatening symptoms.
There is no specific antidote to Letrozole. In general, supportive care, symptomatic treatment and frequent monitoring of vital signs are appropriate.

PRESENTATION
Retzole 2.5mg: Pack of 10 tablets

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
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