Femazol®

Letrozole

FORMS AND PRESENTATION
Femazol®: Film coated tablets: Box of 30.
COMPOSITION
Femazol®: Each film coated tablet contains Letrozole 2.5mg.
Excipients: lactose, croscarmellose sodium, povidone, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, yellow iron oxide, polyethylene glycol, talc.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Endocrine therapy.
ATC code: L02BG04.
The elimination of estrogen-mediated stimulatory effects is a prerequisite for tumor response in cases where the growth of tumor tissue depends on the presence of estrogens. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to estrone (E1) and estradiol (E2). The suppression of estrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.
Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues.
Pharmacokinetic properties
Absorption
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max}: 1 hour fasted versus 2 hours fed; and mean C_{max}: 129 ± 20.3 nmol/L fasted versus 98.7 ± 18.6 nmol/L 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 ± 0.47 L/kg.
Biotransformation and elimination
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 C_{max} were observed.
Formation of minor unidentified metabolites and direct renal and fecal 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 feces. 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.
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.
Age had no effect on the pharmacokinetics of Letrozole.
INDICATIONS
Femazol® is indicated in:
- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with advanced breast cancer.
- Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-estrogen therapy has failed.
- Pre-operative therapy in postmenopausal women with localized hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.

CONTRAINDICATIONS
- Known hypersensitivity to the active substance or to any of the excipients.
- Premenopausal, pregnant or lactating women.
- Patients with severe hepatic impairment (Child-Pugh grade C).
- Pre-operative use of Letrozole is contraindicated if the receptor status is negative or unknown.

PRECAUTIONS
Letrozole is not recommended for use in children as efficacy and safety in this patient group have not been assessed in clinical studies. There are no efficacy data to support the use of Letrozole in men with breast cancer.
Letrozole has not been investigated in patients with creatinine clearance < 10 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of Letrozole.
As Letrozole is a potent estrogen 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 for osteoporosis should be initiated as appropriate and patients treated with Letrozole should be carefully monitored.
Ability to drive and use machines
Since fatigue and dizziness have been observed with the use of Letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines.
PREGNANCY AND LACTATION
Letrozole is contraindicated during pregnancy.
Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in pregnant women exposed to Letrozole.
Letrozole is contraindicated during lactation.
The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are peri-menopausal or who have recently become postmenopausal, until their postmenopausal status is fully established.
There are no adequate data from the use of Letrozole in pregnant women.
Studies in animals have shown reproductive toxicity.
DRUG INTERACTIONS
Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of Letrozole with these drugs does not result in clinically significant drug interactions, even though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolizing Letrozole in vitro.
There was no evidence of other clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).
There is no clinical experience to date on the use of Letrozole in combination with other anti-cancer agents.
Letrozole inhibits in vitro the cytochrome P450-isoenzymes 2A6 and moderately 2C19, however, CYP2A6 does not play a major role in drug metabolism. In in vitro experiments Letrozole was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady-state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. Nevertheless, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.
ADVERSE EFFECTS
Letrozole was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer as well as in the treatment of women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Letrozole in the metastatic and neoadjuvant settings, and approximately 80% of the patients in the adjuvant setting (both Letrozole and tamoxifen arms, at a median treatment duration of 60 months), and approximately 80% of the patients treated following standard adjuvant tamoxifen (both Letrozole and placebo arms, at a median treatment duration of 60 months) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with estrogen deprivation.
The most frequently reported adverse reactions in the clinical studies were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of estrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).
The following adverse drug reactions were reported from clinical studies and from post marketing experience with Letrozole.
Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥ 10%); common (≥ 1% to <10%); uncommon (≥ 0.1% to <1%); rare (≥ 0.01% to < 0.1%); very rare (<0.01%), not known (cannot be estimated from the available data).
- Infections and infestations: Urinary tract infection (uncommon).
- Neoplasms, benign, malignant and unspecified (including cysts and polyps): Tumor pain in metastatic/neoadjuvant setting only (uncommon).
- Blood and the lymphatic system disorders: Leucopenia (uncommon).
- Immune system disorders: Angioedema, anaphylactic reactions (not known).
- Metabolism and nutrition disorders: Anorexia, appetite increase, raised serum cholesterol (common); general edema (uncommon).
- Psychiatric disorders: Depression (common); anxiety including nervousness, and irritability (uncommon).
- Nervous system disorders: Headache, dizziness (common); somnolence, insomnia, memory impairment, dysesthesia including paraesthesia and hypoesthesia, taste disturbance, cerebrovascular accident, carpal tunnel syndrome (uncommon).
- Eye disorders: Cataract, eye irritation, blurred vision (uncommon).
- Cardiac disorders: Palpitations, tachycardia (uncommon).
- Vascular disorders: Thrombophlebitis including superficial and deep thrombophlebitis, hypertension, ischemic cardiac events (uncommon); pulmonary embolism, arterial thrombosis, cerebrovascular infarction (rare).
- Respiratory, thoracic and mediastinal disorders: Dyspnea, cough (uncommon).
- Gastrointestinal disorders: Nausea, vomiting, dyspepsia, constipation, diarrhea (common); abdominal pain, stomatitis, dry mouth (uncommon).
- Hepatobiliary disorders: Increased hepatic enzymes (uncommon); hepatitis (not known).
- Skin and subcutaneous tissue disorders: Alopecia, increased sweating, rash including erythematous, maculopapular, psoriaform and vesicular rash (common); pruritus, dry skin, urticaria (uncommon); toxic epidermal necrolysis, erythema multiforme (not known).
- Musculoskeletal and connective tissue disorders: Arthralgia (very common); myalgia, bone pain, osteoporosis, bone fractures (common); arthritis (uncommon); trigger finger (not known).
- Renal and urinary disorders: Increased urinary frequency (uncommon).
- Reproductive system and breast disorders: Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain (uncommon).
- General disorders and administration site conditions: Hot flushes (very common); fatigue including asthenia and malaise, peripheral edema (common); pyrexia, mucosal dryness, thirst (uncommon).
- Investigations: Weight increase (common); weight loss (uncommon).

DOSAGE AND ADMINISTRATION
Adult and elderly patients
The recommended dose of Femazol® is 2.5 mg once daily. In the adjuvant setting, treatment with Femazol® should continue for 5 years or until tumor relapse occurs, whichever comes first. Following standard adjuvant tamoxifen therapy, treatment with Femazol® should continue for 5 years or until tumor relapse occurs, whichever comes first. In patients with metastatic disease, treatment with Femazol® should continue until tumor progression is evident. Regular monitoring to observe progression during the pre-operative treatment period is recommended. No dose adjustment is required for elderly patients.
Children
Not recommended for use in children.
Patients with hepatic and/or renal impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh grade A and B) or renal impairment (creatinine clearance ≥ 10 mL/min).
OVERDOSAGE
There is no clinical experience of overdosage. 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.
STORAGE CONDITIONS
Store below 30°C.
Keep in original pack in intact conditions.

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This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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