120x160mm

Hitase™
(Letrozole)

Highnoon

COMPOSITION
Hitase 2.5mg Tablet: Each film-coated tablet contains: Letrozole 2.5mg

DESCRIPTION
Hitase tablets for oral administration contains 2.5 mg of Letrozole, a nonsteroidal aromatase inhibitor (inhibitor of oestrogen synthesis).

MECHANISM OF ACTION
Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system; it inhibits the conversion of androgens to oestrogens. It 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 oestrogen 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.
In contrast to ovariectomy, treatment with Letrozole does not lead to an increase in serum Follicle-Stimulating Hormone (FSH).

PHARMACOKINETICS
Letrozole is rapidly and completely absorbed from the gastrointestinal tract. Food decreases the rate but not the extent of absorption. About 60% of letrozole in the circulation is bound to the plasma proteins mainly albumin. Letrozole is rapidly and extensively distributed to tissues. In vitro data suggest that it is metabolised by the cytochrome P450 isoenzymes CYP2A6. Most of an oral dose is slowly metabolised to an inactive carbinol metabolite, which is then excreted as the glucuronide in the urine. Letrozole has a terminal elimination half-life of about 2 days and steady state concentrations occur within 2 to 6 weeks.

INDICATIONS AND USAGE
Letrozole is indicated for:
- Adjuvant Treatment of Early Breast Cancer: Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended Adjuvant Treatment of Early Breast Cancer: Extended adjuvant treatment of early breast cancer in postmenopausal women, who have received 5 years of adjuvant tamoxifen therapy.
- First and Second-Line Treatment of Advanced Breast Cancer: 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 antioestrogen 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.
- 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 post approval 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.
- The treatment should be discontinued at tumour relapse.
- Use in First and Second-Line Treatment of Advanced Breast Cancer: In patients with advanced disease, treatment with Letrozole should continue until tumour 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 greater than or equal to 10 mL/min

CONTRAINDICATIONS
Premenopausal, pregnant or lactating women. Letrozole can cause fetal harm.
Premenopausal endocrine status
Known hypersensitivity to the active substance, or to any of the excipients.

ADVERSE REACTIONS
The reported adverse events are; urinary tract infection, tumour pain, leukopenia, anaphylactic reactions, hypercholesterolaemia, anorexia, appetite increase, depression, anxiety (including nervousness), irritability, headache, dizziness, Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome, cataract, eye irritation, blurred vision, palpitations, tachycardia, ischaemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia), hot flushes, hypertension, thrombophlebitis (including superficial and deep vein thrombophlebitis), ischemic cardiac events, pulmonary embolism, arterial thrombosis, cerebral infarction, dyspnoea, cough, nausea, dyspepsia, constipation, abdominal pain, diarrhoea, vomiting, dry mouth, stomatitis, increased hepatic enzymes, hyperbilirubinemia, jaundice, hepatitis, hyperhidrosis, increased sweating, alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), dry skin, pruritus, urticaria, angioedema, toxic epidermal necrolysis, erythema multiforme, arthralgia, myalgia, bone pain, osteoporosis, bone fractures, arthritis, tendonitis, tendon rupture, trigger finger, pollakiuria, vaginal haemorrhage, vaginal discharge, vulvovaginal dryness, breast pain, fatigue (including asthenia, malaise), peripheral oedema, chest pain, general oedema, pyrexia, mucosal dryness, thirst, weight increase and 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 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.

WARNINGS AND PRECAUTIONS
Menopausal status: In patients whose menopausal status is unclear, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or oestradiol levels should be measured before initiating treatment with Letrozole. Only women of postmenopausal endocrine status should receive Letrozole.

Renal impairment: Letrozole 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.

Hepatic impairment: In patients with severe hepatic impairment (Child-Pugh C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision.

Bone effects: Letrozole is a potent oestrogen-lowering agent. 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. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. 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.

Tendonitis and tendon rupture: Tendonitis and tendon ruptures (rare) may occur. Close monitoring of the patients and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon.

Other warnings: Co-administration of Letrozole with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of Letrozole.

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

USE IN SPECIFIC 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:
Females of reproductive potential should have a pregnancy test prior to starting treatment. 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.

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

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.

Paediatric Use:
The safety and effectiveness in paediatric patients have not been established.

OVERDOSAGE
There is no clinical experience of overdosage only isolated cases of overdose with Letrozole have been reported. 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.

DOSAGE & INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in dry place. Protect from light.

PRESENTATION
Hitase 2.5mg Tablets:
Alu. Alu. Blister pack of 1 x 10's.

ہائیٹیز™
(لیٹروزول)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
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