intez

Letrozole USP tablet

"Please Carefully Read the Full Leaflet"

COMPOSITION

Intez tablet: Each tablet contains Letrozole USP 2.5 mg.

DESCRIPTION

Intez (Letrozole) 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-yl)methylene)dibenzonitrile.

PHARMACEUTICAL DOSAGE FORM AND STRENGTHS

Intez (Letrozole) is presented as 2.5 mg film coated tablet for oral administration.

THERAPEUTIC INDICATIONS

Intez (Letrozole) is indicated for:

Adjuvant Treatment of Early Breast Cancer

Intez (Letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Extended Adjuvant Treatment of Early Breast Cancer

Intez (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 Intez in extended adjuvant treatment of early breast cancer is based on an analysis of disease-free survival in patients treated with Intez for a median of 60 months.

First and Second-Line Treatment of Advanced Breast Cancer

Intez (Letrozole) is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Intez 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 Intez (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. 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 Intez (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 at 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 Intez (Letrozole) 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 Intez (Letrozole) blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis. The dose of Intez (Letrozole) in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose of Intez (Letrozole) for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on Intez (Letrozole) exposure in no cirrhotic 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

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 no tumor- 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.

PHARMACOKINETICS

Absorption and Distribution

Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled Letrozole is recovered in urine. Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than 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. These steady-state levels are maintained over extended periods, however, and continuous accumulation of Letrozole does not occur. Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg).

Metabolism and Excretion

Metabolism to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of Letrozole clearance. Of the radiolabel recovered in urine, at least 75% was the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and 6% was unchanged Letrozole. In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized Letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. In human liver microsomes, Letrozole strongly inhibited CYP2A6 and moderately inhibited CYP2C19.

Pediatric, Geriatric and Race

In the study populations (adults ranging in age from 35 to >80 years), no change in pharmacokinetic parameters was observed with increasing age. Differences in Letrozole pharmacokinetics between adult and pediatric populations have not been studied. Differences in Letrozole pharmacokinetics due to race have not been studied.

Renal Impairment

In a study of registered molecule, volunteers with varying renal function (24-hour creatinine clearance: 9 to 116 mL/min), no effect of renal function on the pharmacokinetics of single doses of 2.5 mg of Letrozole was found. In addition, in a study of 347 patients with advanced breast cancer, about half of whom received 2.5 mg Letrozole and half 0.5 mg Letrozole, renal impairment (calculated creatinine clearance: 20 to 50 mL/min) did not affect steady-state plasma Letrozole concentrations.

Hepatic Impairment

In a study of registered molecule subjects with mild to moderate non-metastatic hepatic dysfunction (e.g., cirrhosis, Child-Pugh classification A and B), the mean AUC values of the volunteers with moderate hepatic impairment were 37% higher than in normal subjects, but still within the range seen in subjects without impaired function.

In a pharmacokinetic study, subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh classification C, which included bilirubins about 2-11 times ULN with minimal to severe ascites) had two-fold increase in exposure (AUC) and 47% reduction in systemic clearance. Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of Letrozole than patients with normal liver function receiving similar doses of this drug.

CONTRAINDICATIONS

Intez may cause fetal harm when administered to a pregnant woman and the clinical benefit to premenopausal women with breast cancer has not been demonstrated. Intez is contraindicated in women who are or may become pregnant. If Intez 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

SPECIAL WARNING AND PRECAUTIONS

Bone Effects
Use of Intez (Letrozole) may cause decreases in bone mineral density (BMD). Consideration should be given for monitoring BMD.

Cholesterol
Consideration should be given for monitoring serum cholesterol.

Hepatic Impairment
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Fatigue and Dizziness
Because fatigue, dizziness and somnolence have been reported with the use of Intez (Letrozole), caution is advised when driving or using machinery until it is known how the patient reacts to Intez (Letrozole) use.

Pregnancy
Intez (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. Intez is contraindicated in women who are or may become pregnant. If Intez 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.

ADVERSE REACTIONS
Non Hematological Adverse Reactions: Hepatotoxicity, Diarrhea, Nausea, Vomiting, Stomatitis, Dyspepsia, Palmar-plantar erythrodysesthesia, Rash, Dry skin, Mucosal inflammation, Back pain, Dyspnea, Skin rash, Insomnia, Alopecia, Fatigue.
Hematological Adverse Reactions: Neutropenia, Thrombocytopenia.

DRUG INTERACTIONS

Tamoxifen
Coadministration of Intez (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 Intez therapy is not impaired if Intez 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 Intez (Letrozole) on Warfarin pharmacokinetics.

Other anticancer agents
There is no clinical experience to date on the use of Intez (Letrozole) in combination with other anticancer agents.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category X. Intez (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. Intez is contraindicated in women who are or may become pregnant. If Intez 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.

Nursing Mothers
It is not known if Letrozole is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Letrozole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Geriatric Use
Adverse reactions were generally reported in elderly patients irrespective of study treatment allocation. However, in comparison to Tamoxifen, no overall differences with regards to the safety and efficacy profiles were observed between elderly patients and younger patients.

Renal Impairment
In a study of registered molecule volunteers with varying renal function (24-hour creatinine clearance: 9 to 116 mL/min), no effect of renal function on the pharmacokinetics of single doses of 2.5 mg of Intez was found. In addition, in a study of 347 patients with advanced breast cancer, about half of whom received 2.5 mg Intez and half 0.5 mg Intez, renal impairment (calculated creatinine clearance: 20 to 50 mL/min) did not affect steady-state plasma Letrozole concentrations.

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In a pharmacokinetic study, subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh classification C, which included bilirubins about 2-11 times ULN with minimal to severe ascites) had two-fold increase in exposure (AUC) and 47% reduction in systemic clearance. Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of Letrozole than patients with normal liver function receiving similar doses of this drug.

OVERDOSAGE

Isolated cases of Intez overdose have been reported. In these instances, the highest single dose ingested was 62.5 mg or 25 tablets. While no serious adverse reactions were reported in these cases, because of the limited data available, no firm recommendations for treatment can be made. However, emesis could be induced if the patient is alert. In general, supportive care and frequent monitoring of vital signs are also appropriate.

PHARMACEUTICAL INFORMATIONS

Storage condition
Store below 30°C, store in a cool & dry place.
Keep away from light.

Keep out of the reach of children.

How supplied
Intez 2.5 mg tablets are supplied in alu-alu blister.
Each 7's box of Intez contains 1X7's tablets.
Each 10's box of Intez contains 1X10's tablets.
Each 14's box of Intez contains 2X7's tablets.
Each 20's box of Intez contains 2X10's tablets.
Each 30's box of Intez contains 3X10's tablets.

Manufactured by

genvio

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