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TREXOZOLA F.C.T

Generic Name : Letrozole 2.5 mg

1 INDICATIONS AND USAGE

1.1 Adjuvant Treatment of Early Breast Cancer

Trexozola tablets are indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

1.2 Extended Adjuvant Treatment of Early Breast Cancer

Trexozola tablets are 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 Trexozola tablets in extended adjuvant treatment of early breast cancer is based on an analysis of diseasefree survival in patients treated with Trexozola tablets for a median of 60 months.

1.3 First and Second-Line Treatment of Advanced Breast Cancer

Trexozola tablets are indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Trexozola tablets are also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of Trexozola tablets is one 2.5 mg tablet administered once a day, without regard to meals.

2.2 Use in Adjuvant Treatment of Early Breast Cancer

In the adjuvant setting, the optimal duration of treatment with Trexozola is unknown. In both the adjuvant study and the postapproval adjuvant study, median treatment duration was 5 years. Treatment should be discontinued at relapse.

2.3 Use in Extended Adjuvant Treatment of Early Breast Cancer

In the extended adjuvant setting, the optimal treatment duration with Trexozola tablets 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 Trexozola tablets 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.

2.4 Use in First and Second-Line Treatment of Advanced Breast Cancer

In patients with advanced disease, treatment with Trexozola tablets should continue until tumor progression is evident.

2.5 Use in Hepatic Impairment

No dosage adjustment is recommended for patients with mild to moderate hepatic impairment, although Trexozola tablets blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis. The dose of Trexozola tablets in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50% *[see Warnings and Precautions (5.4)]*. The recommended dose of Trexozola tablets for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on Trexozola tablets exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

2.6 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. *[see Clinical Pharmacology (10.3)]*.

3 DOSAGE FORMS AND STRENGTHS

2.5 mg tablets : Yellow colored, round biconvex film-coated tablets.

4 CONTRAINDICATIONS

• Pregnancy : Letrozole can cause fetal harm *[see Use in Specific Populations (8.1)]*.

• Known hypersensitivity to the active substance, or to any of the excipients *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

5.2 Bone Effects

Use of Trexozola tablets may cause decreases in bone mineral density (BMD). Consideration should be given to monitoring BMD. Results of a safety study to evaluate safety in the adjuvant setting comparing the effect on lumbar spine (L2-L4) BMD of adjuvant treatment with Trexozola to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) (P<0.0001) *[see Adverse Reactions (6)]*. Updated results from the BMD substudy (MA-17B) in the extended adjuvant setting demonstrated that at 2 years patients receiving letrozole had a median decrease from baseline of 3.8% in hip BMD compared to a median decrease of 2.0% in the placebo group. The changes from baseline in lumbar spine BMD in Trexozola and placebo treated groups were not significantly different *[see Adverse Reactions (6)]*.

In the adjuvant trial (BIG 1-98) the incidence of bone fractures at any time after randomization was 14.7% for Trexozola and 11.4% for tamoxifen at a median follow-up of 96 months. The incidence of osteoporosis was 5.1% for Trexozola and 2.7% for tamoxifen [see Adverse Reactions (6)]. In the extended adjuvant trial (MA-17), the incidence of bone fractures at any time after randomization was 13.3% for Trexozola and 7.8% for placebo at a median follow-up of 62 months. The incidence of new osteoporosis was 14.5% for Trexozola and 7.8% for placebo *[see Adverse Reactions (6)]*.

5.3 Cholesterol

Consideration should be given to monitoring serum cholesterol. In the adjuvant trial (BIG 1-98), hypercholesterolemia was reported in 52.3% of Trexozola patients and 28.6% of tamoxifen patients. Grade 3-4 hypercholesterolemia was reported in 0.4% of Trexozola patients and 0.1% of tamoxifen patients. Also in the adjuvant setting, an increase of greater than or equal to 1.5 × 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 × ULN) in 155/1843 (8.4%) patients on Trexozola vs 71/1840 (3.9%) patients on tamoxifen. Lipid lowering medications were required for 29% of patients on Trexozola and 20% on tamoxifen *[see Adverse Reactions (6)]*.

5.4 Hepatic Impairment

Subjects with cirrhosis and severe hepatic impairment who were dosed with 2.5 mg of Trexozola tablets experienced approximately twice the exposure to Trexozola tablets as healthy volunteers with normal liver function *[see Clinical Pharmacology (10.3)]*. Therefore, a dose reduction is recommended for this patient population. The effect of hepatic impairment on Trexozola tablets exposure in cancer patients with elevated bilirubin levels has not been determined. *[see Dosage and Administration (2.5)]*.

5.5 Fatigue and Dizziness

Because fatigue, dizziness, and somnolence have been reported with the use of Trexozola tablets, caution is advised when driving or using machinery until it is known how the patient reacts to Trexozola tablets use.

5.6 Laboratory Test Abnormalities

No dose-related effect of letrozole tablets on any hematologic or clinical chemistry parameter was evident. Moderate decreases in lymphocyte counts, of uncertain clinical significance, were observed in some patients receiving Trexozola tablets 2.5mg. This depression was transient in about half of those affected. Two patients on Trexozola tablets developed thrombocytopenia; relationship to the study drug was unclear. Patient withdrawal due to laboratory abnormalities, whether related to study treatment or not was infrequent.

5.7 Embryo-Fetal Toxicity

Based on post-marketing reports, findings from animal studies and the mechanism of action, Trexozola tablets can cause fetal harm and is contraindicated for use in pregnant women. In post-marketing reports, use of Trexozola during pregnancy resulted in cases of spontaneous abortions and congenital birth defects. Trexozola caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below the maximum recommended human dose (MHRD) on a mg/m basis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during therapy with Trexozola tablets and for at least 3 weeks after the last dose *[see Postmarketing Experience (6.1), Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (10.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

Bone effects *[see Warnings and Precautions (5.2)]*

Increases in cholesterol *[see Warnings and Precautions (5.3)]*

Fatigue and Dizziness *[see Warnings and Precautions (5.5)]*

6.1 Post marketing Experience

The following adverse reactions have been identified during postapproval use of Trexozola tablets.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

• Eye Disorders : blurred vision

• Hepatobiliary Disorders : increased hepatic enzymes, hepatitis

• Immune System Disorders : anaphylactic reactions, hypersensitivity reactions

• Nervous System Disorders : carpal tunnel syndrome, trigger finger

• Pregnancy : spontaneous abortions, congenital birth defects

• Skin and subcutaneous disorders : angioedema, toxic epidermal necrolysis, erythema multiforme

To report SUSPECTED ADVERSE REACTIONS contact Human Pharmacovigilance Department – Egyptian Pharmaceutical Vigilance Center (EPVC)- Egyptian Drug Authority (EDA) 21 Abd Elaziz Al Souad st. – Manial El-Roda – Cairo, PO Box : 11451

Tel : +2 02 23648046 / +2 02 23640368 / +2 02 23684381 Extension (Tel) : 1303 Extension (Fax) : 1300

Fax : +2 02 23684194 ; Website: www.epvc.gov.eg; e-mail : pv.center@eda.mohealth.gov.eg

7 DRUG INTERACTIONS

Tamoxifen

Coadministration of Trexozola tablets and tamoxifen 20 mg daily resulted in a reduction of Trexozola 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 Trexozola tablets therapy is not impaired if Trexozola tablets are administered immediately after tamoxifen.

Cimetidine

A pharmacokinetic interaction study with cimetidine (study P004) showed no clinically significant effect on Trexozola pharmacokinetics.

Warfarin

An interaction study (P017) with warfarin showed no clinically significant effect of Trexozola on warfarin pharmacokinetics.

Other anticancer agents

There is no clinical experience to date on the use of Trexozola tablets in combination with other anticancer agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on post-marketing reports, findings from animal studies and the mechanism of action, Trexozola tablets can cause fetal harm and are contraindicated for use in pregnant women. In post-marketing reports, use of Trexozola during pregnancy resulted in cases of spontaneous abortions and congenital birth defects; however, the data are insufficient to inform a drug-associated risk. *[see Contraindications (4), Warnings and Precautions (5.7), Postmarketing Experience (6.1), and Clinical Pharmacology (10.1)]*.

In animal reproduction studies, administration of Trexozola to pregnant animals during organogenesis resulted in increased post-implantation pregnancy loss and resorption, fewer live fetuses, and fetal malformation affecting the renal and skeletal systems in rats and rabbits at doses approximately 0.1 times the daily maximum recommended human dose (MRHD) on a mg/m basis.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

It is not known if Trexozola is present in human milk. There are no data on the effects of Trexozola on the breastfed infant or milk production. Exposure of lactating rats to Trexozola was associated with impaired reproductive perfor-

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mance of the male offspring . Because of the potential for serious adverse reactions in breastfed infants from Trexozola, advise lactating women not to breastfeed while taking Trexozola and for at least 3 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, Trexozola tablets can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)] . Females of reproductive potential should have a pregnancy test prior to starting treatment with Trexozola tablets.

Contraception

Females

Based on animal studies, Trexozola tablets can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Trexozola tablets and for at least 3 weeks after the last dose.

Infertility

Females

Based on studies in female animals, Trexozola tablets may impair fertility in females of reproductive potential.

Males

Based on studies in male animals, Trexozola tablets may impair fertility in males of reproductive potential.

8.4 Pediatric Use

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

8.5 Geriatric Use

The median age of patients in all studies of first-line and second-line treatment of metastatic breast cancer was 64-65 years. About 1/3 of the patients were greater than or equal to 70 years old. In the first-line study, patients greater than or equal to 70 years of age experienced longer time to tumor progression and higher response rates than patients less than 70.

9 OVERDOSAGE

Isolated cases of Trexozola tablets 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. In single-dose studies, the highest dose used was 30 mg, which was well tolerated; in multiple-dose trials, the largest dose of 10 mg was well tolerated.

Lethality was observed in mice and rats following single oral doses that were equal to or greater than 2,000 mg/kg (about 4,000 to 8,000 times the daily maximum recommended human dose on a mg/m basis); death was associated with reduced motor activity, ataxia and dyspnea. Lethality was observed in cats following single IV doses that were equal to or greater than 10 mg/kg (about 50 times the daily maximum recommended human dose on a mg/m basis); death was preceded by depressed blood pressure and arrhythmias.

10 CLINICAL PHARMACOLOGY

10.1 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 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.

10.2 Pharmacodynamics

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg letrozole tablets 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. No clinically-relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole tablets 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 letrozole tablets 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.

10.3 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).

Elimination

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 inhibited CYP2A6 and CYP2C19, however, the clinical significance of these findings is unknown.

Specific Populations

Pediatric, Geriatric and Race : In the study populations (adults ranging in age from 35 to greater than 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 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 tablets was found. In addition, in a study (AR/BC2) of 347 patients with advanced breast cancer, about half of whom received 2.5 mg letrozole tablets and half 0.5 mg letrozole tablets, renal impairment (calculated creatinine clearance : 20 to 50 mL/min) did not affect steady-state plasma letrozole concentrations.

Hepatic Impairment : In a study of subjects with mild to moderate non-metastatic hepatic dysfunction (e.g., cirrhosis, Child-Pugh classification A and B), the mean area under curve (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. *[see Dosage and Administration (2.5)]*

11 HOW SUPPLIED/STORAGE AND HANDLING

2.5 milligram tablets

Carton box contains (Al / transparent colourless PVC) strip contains 10 film coated tablets.

Store at temperature not exceeding 30°C in dry place

12 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during Trexozola tablets therapy and for at least 3 weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with Trexozola tablets [see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.3)].

Lactation

Advise women not to breastfeed during Trexozola tablets treatment and for at least 3 weeks after the last dose [see Use in Specific Populations (8.2)].

Infertility

Advise females and males of reproductive potential of the potential for reduced fertility from Trexozola tablets [see Use in Specific Populations (8.3)].

Fatigue and Dizziness

Since fatigue and dizziness have been observed with the use of Trexozola tablets and somnolence was uncommonly reported, caution is advised when driving or using machinery.

Bone Effects

Consideration should be given to monitoring bone mineral density.

13 Shelf Life : 2 years

14 Inactive Ingredients : Microcrystalline cellulose (Avicel PH102), Lactose monohydrate, Maize starch, Sodium starch glycolate, Magnesium stearate and Colloidal silicon dioxide (Aerosil 200). Film coat: Opadry II yellow code (85F32410), Polyvinyl alcohol (part. Hydrolyzed), Titanium dioxide (C.I.N°. 77891), Macrogol 4000, Talc and Iron oxide yellow (C.I.N° 77492).

Produced by : Technopharma Egypt

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