Estrodex® 2.5mg

(Letrozole)
Film Coated Tablets

Composition

Each Film Coated Tablet contains 2.5mg Letrozole.
Excipients: Lactose monohydrate, Maize starch, Hypromellose (Type 2910), Purified water, Cellulose microcrystalline, Sodium starch glycolate (Type A), Colloidal anhydrous silica, Magnesium stearate, Opadry 03B82927 Yellow.

Concentration and Pharmaceutical Form

2.5mg film-coated tablets.

Indications

- Adjuvant treatment of postmenopausal women with early breast cancer (positive or unknown oestrogen or progesterone receptor status).
- Adjuvant treatment of postmenopausal women with early breast cancer (positive or unknown oestrogen or progesterone receptor status) who have received 5 years of adjuvant tamoxifen therapy (extended adjuvant therapy).
- Treatment of advanced breast cancer in postmenopausal women with positive oestrogen or progesterone receptor status, or with unknown receptor status, in whom postmenopausal status is natural or artificially induced.

Dosage and Administration Adults and elderly patients

The recommended dose of **Estrodex** is 2.5 mg once daily. It may be taken with or without food. Adjuvant therapy with **Estrodex** should be given for 5 years, or until relapse occurs. Experience to date from clinical studies covers a period of up to 2.5 years (median) only.
Extended adjuvant therapy with **Estrodex** following 5 years of tamoxifen therapy should be continued until relapse occurs. Experience to date from clinical studies covers a period of up to 2.5 years (median) only.
In patients with advanced breast cancer, treatment should continue until tumor progression is evident.

Dosage in patients with hepatic and/or renal impairment

No dosage adjustment is necessary in patients with hepatic or renal impairment (creatinine clearance>10 ml/minute; see Warnings and Precautions).

Paediatric use

Estrodex must not be given to children or adolescents.

Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- Premenopausal endocrine status. Pregnancy and lactation (see Pregnancy and Lactation and Preclinical data).

Warnings and Precautions

In patients whose postmenopausal status seems unclear, LH, FSH and/or oestradiol levels must be assessed before initiating treatment in order to clearly establish menopausal status. Letrozole should not be given concurrently with drugs containing oestrogen because the latter would eliminate the pharmacological efficacy of Letrozole. Letrozole reduces circulating oestrogen levels and long-term use may therefore result in a reduction in bone mineral density. In women with osteoporosis, or at risk of osteoporosis, bone density should be assessed by bone densitometry at the start of adjuvant treatment with Letrozole, and at regular intervals thereafter. Measures should be initiated where necessary to prevent or treat osteoporosis, and the patients in question should be closely monitored.

Renal impairment

Letrozole has not been investigated in women with creatinine clearance < 10 ml/minute. The benefit to such patients should be carefully weighed against the possible risks before initiation of treatment.

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately twice as high as in healthy volunteers. Such patients should therefore be closely monitored. Clinical experience with repeated dosage is not available.

Interactions

Letrozole is a substrate of CYP3A4. While it is unlikely to have an effect on substances that are metabolized by CYP3A4, such substances could influence the biotransformation of Letrozole by CYP3A4. Letrozole inhibits CYP2A6 and, to a lesser extent, CYP2C19 in vitro. Caution is therefore required when concomitantly administering substances with a narrow therapeutic index whose availability is primarily dependent on these isoenzymes. CYP2A6 does not play a major role in drug metabolism. In vitro experiments showed that Letrozole, at plasma concentrations approximately 100 times higher than those observed at steady-state, did not impair the metabolism of diazepam (a substrate of CYP2C19). Clinically relevant interactions with CYP2C19 are therefore unlikely.
Clinical interaction studies with cimetidine and warfarin showed that co-administration of Letrozole with these substances does not result in clinically significant drug interactions. Concomitant administration of Letrozole with tamoxifen (20 mg/day) resulted in a decrease in plasma Letrozole levels by 38% on average. Letrozole had no effect on plasma tamoxifen levels. There is no clinical experience of the use of Letrozole in combination with other cytostatic agents.

Pregnancy and Lactation

Letrozole is contraindicated during pregnancy and lactation (see Contraindications and Preclinical data).
The physician must inform women of child-bearing potential, and women who are perimenopausal or who have recently become postmenopausal, of the necessity of adequate contraception. There are insufficient data on use in pregnant women. Animal studies have shown evidence of reproductive toxicity (see Preclinical data).

Effects on ability to drive and use machines

Fatigue and dizziness have been observed in association with Letrozole, and there have been occasional reports of drowsiness. Caution is therefore required when driving vehicles or using machines.

Adverse effects

Adverse effects were seen in approximately 70-75% of patients receiving adjuvant treatment, and in approximately one-third of those undergoing extended adjuvant treatment or being treated for advanced breast cancer. The adverse effects reported were usually mild to moderate in nature.

The most frequently reported adverse effects in the clinical studies were hot flushes (10.9%), arthralgia (13.1%), nausea (6.9%) and fatigue (5.0%). Many adverse effects can be attributed to the consequences of oestrogen deprivation (e.g. hot flushes, hair loss and vaginal bleeding).
The following adverse effects were reported with adjuvant treatment in the Letrozole group and tamoxifen group, regardless whether or not there was any connection to treatment: thromboembolic events (1.2% and 3.0%), angina pectoris (0.8% and 0.8%), myocardial infarction (0.5% and 0.4%), heart failure (0.8% and 0.3%), bone fractures (6.3% and 4.7%).
The following adverse effects were observed during clinical studies and in the post-marketing phase: Frequency estimates:
Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10 000)
Infections
Uncommon: Urinary tract infection.
Blood and lymphatic system
Uncommon: Leucopenia.
Endocrine disorders
Very common: Hot flushes (10.9%).
Metabolism and nutrition disorders
Common: Loss of appetite, increased appetite, hypercholesterolemia, weight gain.
Uncommon: Weight loss.
Psychiatric disorders
Common: Depression.
Uncommon: anxiety, nervousness, irritability.
Nervous system disorders
Common: Headache, dizziness.
Uncommon: Drowsiness, insomnia, impairment of memory, dysaesthesias, paraesthesias, hypo-aesthesias, dysgeusia.
Eye disorders
Uncommon: Cataract, eye irritation, blurred vision.
Cardiovascular system
Common: Hypertension, thromboembolism.
Uncommon: Palpitations, tachycardia, superficial and deep thrombophlebitis, hypotension, stroke, ischaemic heart disease, angina pectoris, myocardial infarction, heart failure.
Respiratory tract disorders
Uncommon: Dyspnoea, cough.
Gastrointestinal disorders
Common: Nausea, vomiting, dyspepsia, constipation, diarrhoea.
Uncommon: Abdominal pain, stomatitis, dry mouth, mucosal dryness.
Hepatobiliary disorders
Uncommon: Increased hepatic enzymes.
Skin
Common: Hair loss, increased sweating, erythematous, maculopapular, psoriasiform and vesicular skin rashes.
Uncommon: Pruritus, dry skin, urticaria. Musculoskeletal system
Very common: Arthralgia (13.1%).
Common: Myalgia, bone pain, osteoporosis, bone fractures.
Uncommon: Arthritis.
Renal and urinary disorders
Uncommon: Increased urinary frequency.
Reproductive system and breast disorders
Uncommon: Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain.
General disorders
Common: Fatigue, asthenia, malaise, peripheral oedema, generalized oedema.
Uncommon: Fever, thirst.

Overdose

Isolated cases of overdosage with Letrozole have been reported. No specific treatment is known. Management should be symptomatic and supportive.

Preclinical data

Neither in vitro nor in vivo investigations of mutagenic potential revealed any evidence of genotoxicity. In a conventional carcinogenesis study, doses of 0.6 to 60 mg/kg/day (about 1 to 100 times the daily maximum human dose on a mg/m2 basis) were administered by gavage in mice for up to 2 years. This study revealed a dose-related increase in the incidence of benign ovarian stromal tumors. The incidence of combined hepatocellular adenoma and carcinoma showed a significant trend in female mice when the high-dose group was excluded due to low survival. In a separate study, plasma AUC 0-12 hour levels in mice given a dose of 0.6 mg/kg/day were equivalent to 0.4 times the AUC 0-24 hour level in breast-cancer patients given the recommended dose. In a 104 week rat carcinogenicity study, no treatment-related tumors were found. In female rats, a reduced incidence of benign and malignant mammary tumors was determined at all doses of letrozole. Oral administration of letrozole to pregnant rats resulted in a slight increase in the incidence of fetal malformations in the treated animals. However, it was not possible to determine whether this was an indirect consequence of the pharmacological characteristics (inhibition of oestrogen biosynthesis) or a direct effect of letrozole per se. Preclinical observations were limited to those associated with the acknowledged pharmacological effect. These were thus the only safety concerns regarding use in humans that arose from the animal studies. Letrozole is therefore contraindicated during pregnancy and lactation (see Contraindications).

Shelf-life

Do not use after the expiry date printed on the pack.

Storage

Store below 30°C, protected from moisture.
Keep out of reach of children.

Pack sizes

30 film-coated tablets per pack.

Sep., 2011
I-0043-LM0-R0/EE

This is a medicament:

- A medicament is a product that 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.
- Keep out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

Al Taqaddom Pharmaceutical Industries, Amman - Jordan

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