EMVIA®

Letrozole film-coated tablets

1. DESCRIPTION

Emvia® tablets for oral administration contain 2.5 mg of letrozole, a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis).

Inactive ingredients include: Lactose monohydrate; Maize starch; Hypromellose; Microcrystalline cellulose ; Sodium starch glycolate; Colloidal anhydrous silica and Magnesium stearate.

The film coating solution consists of: Hypromellose; Titanium dioxide; Yellow iron oxide ; Polyethylene glycol and Talc.

Emvia® 2.5 mg tablets are yellow, round, biconvex, film-coated, plain on both sides.

2. INDICATIONS AND USAGE

Adjuvant Treatment of Early Breast Cancer: Emvia® is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Extended Adjuvant Treatment of Early Breast Cancer: Emvia® is indicated for the 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: Emvia® is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Emvia® is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

3. 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. The planned duration of treatment in the study 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. In the final updated analysis conducted at a median follow-up of 62 months, the median treatment duration was 60 months. 71 % 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 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. 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.

Use in Renal Impairment: No dosage adjustment is required for patients with renal impairment if creatinine clearance is ≥ 10 mL/min.

4. SIDE EFFECTS

The most serious adverse reactions from the use of letrozole are:

- Bone effects [see PRECAUTIONS]
- Increases in cholesterol [see PRECAUTIONS]

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Treatment of Early Breast Cancer: The median treatment duration of adjuvant treatment was 60 months and the median duration of follow-up for safety was 73 months for patients receiving letrozole and tamoxifen.

Certain adverse reactions were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs.

Most adverse reactions reported (approximately 75% of patients reporting 1 or more AE) were Grade 1 or Grade 2 applying the Common Toxicity Criteria Version 2.0/ Common Terminology Criteria for Adverse Events, version 3.0.

When considering all grades during study treatment, a higher incidence of events was seen for letrozole regarding fractures (10.1% vs 7.1%), myocardial infarctions (1.0% vs 0.5%) and arthralgia (25.2% vs 20.4%) (Letrozole vs Tamoxifen respectively). A higher incidence was seen for tamoxifen regarding thromboembolic events (2.1% vs 3.6%), endometrial hyperplasia/cancer (0.3% vs 2.9%) and endometrial proliferation disorders (0.3% vs 1.8%) (Letrozole vs Tamoxifen respectively).

At a median follow up of 73 months, a higher incidence of events was seen for letrozole (13.8%) than for tamoxifen (10.5%) regarding fractures. A higher incidence was seen for tamoxifen compared to letrozole regarding thromboembolic events (4.5% vs 2.9%) and endometrial hyperplasia or cancer (2.9% vs 0.4%) (Tamoxifen vs Letrozole respectively).

Bone Study: Results of a phase 3 safety trial in 262 post menopausal women with resected receptor positive early breast cancer in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (BMD) of adjuvant treatment with letrozole 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%) ($P < 0.0001$). No patients with a normal BMD at baseline became osteoporotic over the 2 years and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review). The results for total hip BMD were similar, although the differences between the two treatments were less pronounced. During the 2 year period, fractures were reported by 4 of 103 patients (4%) in the letrozole arm and 6 of 97 patients (6%) in the tamoxifen arm.

Lipid Study: In a phase 3 safety trial in 262 post menopausal women with resected receptor positive early breast cancer at 24 months comparing the effects on lipid profiles of adjuvant letrozole to tamoxifen, 12% of patients on letrozole had at least one total cholesterol value of a higher CTCAE grade than at baseline compared with 4% of patients on tamoxifen.

Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months: The median duration of extended adjuvant treatment was 24 months and the median duration of follow-up for safety was 28 months for patients receiving letrozole and placebo.

Most adverse reactions reported were Grade 1 and Grade 2 based on the Common Toxicity Criteria Version 2.0. In the extended adjuvant setting, the reported drug-related adverse reactions that were significantly different from placebo were hot flashes, arthralgia/arthritis and myalgia.

Based on a median follow-up of patients for 28 months, the incidence of clinical fractures from the core randomized study in patients who received letrozole was 5.9% (152) and placebo was 5.5% (142). The incidence of self-reported osteoporosis was higher in patients who received letrozole 6.9% (176) than in patients who received placebo 5.5% (141). Bisphosphonates were administered to 21.1% of the patients who received letrozole and 18.7% of the patients who received placebo. The incidence of cardiovascular ischemic events from the core randomized study was comparable between patients who received letrozole 6.8% (175) and placebo 6.5% (167).

Lipid Sub-study: In the extended adjuvant setting, based on a median duration of follow-up of 62 months, there was no significant difference between letrozole and placebo in total cholesterol or in any lipid fraction at any time over 5 years. Use of lipid lowering drugs or dietary management of elevated lipids was allowed.

First-Line Treatment of Advanced Breast Cancer: A total of 455 patients were treated for a median time of exposure of 11 months. The incidence of adverse reactions was similar for letrozole and tamoxifen. The most frequently reported adverse reactions were bone pain, hot flushes, back pain, nausea, arthralgia and dyspnea.

Discontinuations for adverse reactions other than progression of tumor occurred in 10/455 (2%) of patients on letrozole and in 15/455 (3%) of patients on tamoxifen.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with letrozole 2.5 mg or tamoxifen 20 mg in the first-line treatment study are: Fatigue, chest pain, peripheral edema, pain, weakness, decreased weight, hot flushes, hypertension, nausea, constipation, diarrhea, vomiting, influenza, urinary tract infection, post-mastectomy lymphedema, anorexia, bone pain, back pain, arthralgia, pain in limb, headache, insomnia, breast pain, dyspnea, cough and chest wall pain.

Other less frequent (≤ 2%) adverse reactions considered consequential for both treatment groups, included peripheral thromboembolic events, cardiovascular events and cerebrovascular events. Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis and pulmonary embolism. Cardiovascular events included angina, myocardial infarction, myocardial ischemia and coronary heart disease. Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic strokes and development of hemiparesis.

Second- Line Treatment of Advanced Breast Cancer: Study discontinuations in the megestrol acetate comparison study for adverse reactions other than progression of tumor were 5/188 (2.7%) on letrozole 0.5 mg, 4/174 (2.3%) on letrozole 2.5 mg and 15/190 (7.9%) on megestrol acetate. There were fewer thromboembolic events at both letrozole doses than on the megestrol acetate arm (0.6% vs 4.7%). There was also less vaginal bleeding (0.3% vs 3.2%) on letrozole than on megestrol acetate. In the aminoglutethimide comparison study, discontinuations for reasons other than progression occurred in 6/193 (3.1%) on 0.5 mg letrozole, 7/185 (3.8%) on 2.5 mg letrozole and 7/178 (3.9%) of patients on aminoglutethimide.

Comparisons of the incidence of adverse reactions revealed no significant differences between the high and low dose letrozole groups in either study. Most of the adverse reactions observed in all treatment groups were mild to moderate in severity and it was generally not possible to distinguish adverse reactions due to treatment from the consequences of the patient's metastatic breast cancer, the effects of estrogen deprivation or intercurrent illness.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with letrozole 0.5 mg, letrozole 2.5 mg, megestrol acetate or aminoglutethimide in the two controlled trials are: Fatigue, chest pain, peripheral edema, asthenia, weight increase, hypertension, nausea, constipation, diarrhea, vomiting, abdominal pain, anorexia, dyspepsia, viral infection, hypercholesterolemia, musculoskeletal, arthralgia, headache, somnolence, dizziness, dyspnea, coughing, hot flushes, rash and pruritus.

Other less frequent (< 5%) adverse reactions considered consequential and reported in at least 3 patients treated with letrozole included hypercalcemia, fracture, depression, anxiety, pleural effusion, alopecia, increased sweating and vertigo.

First and Second-Line Treatment of Advanced Breast Cancer: In the combined analysis of the first and second-line metastatic trials and post-marketing experiences, other adverse reactions that were reported were: Cataract, eye irritation, palpitations, cardiac failure, tachycardia, dysesthesia, arterial thrombosis, memory impairment, irritability, nervousness, urticaria, increased urinary frequency, leukopenia, stomatitis cancer pain, pyrexia, vaginal discharge, appetite increase, dryness of skin and mucosa (including dry mouth) and disturbances of taste and thirst.

Post-marketing Experience: Cases of blurred vision, increased hepatic enzymes, angioedema, anaphylactic reactions, toxic epidermal necrolysis, erythema multiforme and hepatitis have been reported.

5. DRUG INTERACTIONS

Tamoxifen: Coadministration of 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 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.

6. PRECAUTIONS

Bone Effects: Use of letrozole may cause decreases in bone mineral density (BMD). Consideration should be given to monitoring BMD.

Cholesterol: Consideration should be given to monitoring serum cholesterol.

Hepatic Impairment: A dose reduction is recommended for this patient population.

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

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

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility: A conventional carcinogenesis study in mice at doses of 0.6 to 60 mg/kg/day (about 1 to 100 times the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years 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 females when the high dose group was excluded due to low survival. In a separate study, plasma AUC0-12hr levels in mice at 60 mg/kg/day were 55 times higher than the AUC0-24hr level in breast cancer patients at the recommended dose. The carcinogenicity study in rats at oral doses of 0.1 to 10 mg/kg/day (about 0.4 to 40 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years also produced an increase in the incidence of benign ovarian stromal tumors at 10 mg/kg/day. Ovarian hyperplasia was observed in females at doses equal to or greater than 0.1 mg/kg/day. At 10 mg/kg/day, plasma AUC0-24hr levels in rats were 80 times higher than the level in breast cancer patients at the recommended dose.

Letrozole was not mutagenic in *in vitro* tests (*Ames* and *E.coli* bacterial tests) but was observed to be a potential clastogen in *in vitro* assays. Letrozole was not clastogenic *in vivo* (micronucleus test in rats). Studies to investigate the effect of letrozole on fertility have not been conducted; however, repeated dosing caused sexual inactivity in females and atrophy of the reproductive tract in males and females at doses of 0.6, 0.1 and 0.03 mg/kg in mice, rats and dogs respectively (about one, 0.4 and 0.4 the daily maximum recommended human dose on a mg/m^2 basis, respectively).

Use In Specific Populations

Pregnancy: Pregnancy Category X. 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. Letrozole is contraindicated in women who are or may become pregnant. If this drug 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.

Physicians should discuss the need for adequate contraception with women who are recently menopausal. Contraception should be used until postmenopausal status is clinically well established.

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: 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 ≥ 70 years old.

In the extended adjuvant setting, no overall differences in safety or efficacy were observed between older patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In the adjuvant setting, more adverse reactions were generally reported in elderly patients. However, in comparison to tamoxifen, no overall differences with regards to the safety and efficacy profiles were observed between elderly patients and younger patients.

7. OVERDOSE

Isolated cases of letrozole 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.

8. CONTRAINDICATIONS

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. Letrozole is contraindicated in women who are or may become pregnant. If letrozole 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.

9. CLINICAL STUDIES

Updated Adjuvant Treatment of Early Breast Cancer: In a multicenter study enrolling over 8,000 postmenopausal women with resected, receptor-positive early breast cancer, one of the following treatments was randomized in a double-blind manner:

Option 1: A. Tamoxifen for 5 years. B. Letrozole for 5 years. C. Tamoxifen for 2 years followed by letrozole for 3 years. D. Letrozole for 2 years followed by tamoxifen for 3 years

Option 2: A. Tamoxifen for 5 years. B. Letrozole for 5 years.

The study in the adjuvant setting, BIG 1-98 was designed to answer two primary questions: whether letrozole for 5 years was superior to tamoxifen for 5 years (Primary Core Analysis) and whether switching endocrine treatments at 2 years was superior to continuing the same agent for a total of 5 years (Sequential Treatments Analysis). The primary endpoint of this trial was disease-free survival (DFS) (i.e., interval between randomization and earliest occurrence of a local, regional or distant recurrence or invasive contralateral breast cancer or death from any cause). The secondary endpoints were overall survival (OS), systemic disease-free survival (SDFS), invasive contralateral breast cancer, time to breast cancer recurrence (TBR) and time to distant metastasis (TDM).

The Primary Core Analysis (PCA) included all patients and all follow-up in the monotherapy arms in both randomization options, but follow-up in the two sequential treatments arms was truncated 30 days after switching treatments. The PCA was conducted at a median treatment duration of 24 months and a median follow-up of 26 months. Letrozole was superior to tamoxifen in all endpoints except overall survival and contralateral breast cancer [e.g., DFS: hazard ratio, HR 0.79; 95% CI (0.68, 0.92); P=0.002; SDFS: HR 0.83; 95% CI (0.70, 0.97); TDM: HR 0.73; 95% CI (0.60, 0.88); OS: HR 0.86; 95% CI (0.70, 1.06)].

Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months: A double-blind, randomized, placebo-controlled trial of letrozole was performed in over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who were disease-free after 5 years of adjuvant treatment with tamoxifen.

The planned duration of treatment for patients in the study was 5 years, but the trial was terminated early because of an interim analysis showing a favorable letrozole effect on time without recurrence or contralateral breast cancer. At the time of unblinding, women had been followed for a median of 28 months, 30% of patients had completed 3 or more years of follow-up and less than 1% of patients had completed 5 years of follow-up.

First-Line Treatment of Advanced Breast Cancer: A randomized, double-blind, multinational trial compared letrozole 2.5 mg with tamoxifen 20 mg in 916 postmenopausal patients with locally advanced (Stage IIIB or loco-regional recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer. Time to progression (TTP) was the primary endpoint of the trial.

Letrozole was superior to tamoxifen in TTP and rate of objective tumor response: median time to progression was 9.4 months for letrozole 2.5 mg and 6 months for tamoxifen 20 mg (HR 0.72; 95% CI (0.62, 0.83); P< 0.0001). The objective response rate (CR + PR) was 32% for letrozole 2.5 mg and 21% for tamoxifen 20 mg (HR 1.77; 95% CI (1.31, 2.39); P= 0.0002). There was no significant difference between treatment arms in overall survival.

Second-Line Treatment of Advanced Breast Cancer: Two large randomized, controlled, multinational trials were conducted in patients with advanced breast cancer who had progressed despite antiestrogen therapy. Patients were randomized to letrozole 0.5 mg daily, letrozole 2.5 mg daily or a comparator (megestrol acetate 160 mg daily in one study; and aminoglutethimide 250 mg b.i.d. with corticosteroid supplementation in the other study). In each study over 60% of the patients had received therapeutic antiestrogens and about one-fifth of these patients had had an objective response. The megestrol acetate controlled study was double-blind; the other study was open label.

Confirmed objective tumor response (complete response plus partial response) was the primary endpoint of the trials.

The results for the first trial, with a minimum follow-up of 15 months, compared letrozole 0.5 mg, letrozole 2.5 mg and megestrol acetate 160 mg daily. The objective response rate (CR + PR) was 11.7% for letrozole 0.5 mg (n=188), 23.6% for letrozole 2.5 mg (n=174) and 16.3% for megestrol acetate (n=190). The median duration of response was 552 days for letrozole 0.5 mg, not reached for letrozole 2.5 mg and 561 days for megestrol acetate. The median time to progression was 154 days for letrozole 0.5 mg, 170 days for letrozole 2.5 mg and 168 days for megestrol acetate. The median survival was better with letrozole 2.5 mg: 730 days vs. 633 days for letrozole 0.5 mg and 659 days for megestrol acetate. The two-sided P-value was 0.004.

The results for the study comparing letrozole to aminoglutethimide, with a minimum follow-up of 9 months, showed a significant decrease in the risk of progression with letrozole 2.5 mg vs. aminoglutethimide. The objective response rate (CR + PR) was 17.6% for letrozole 0.5 mg (n=193), 18.4% for letrozole 2.5 mg (n=185) and 12.3% for aminoglutethimide (n=179). The median duration of response was 619 days for letrozole 0.5 mg, 706 days for letrozole 2.5 mg and 450 days for aminoglutethimide. The median time to progression was 103 days for letrozole 0.5 mg, 123 days for letrozole 2.5 mg and 112 days for aminoglutethimide. The median survival was better with letrozole 2.5 mg: 792 days vs. 636 days for letrozole 0.5 mg and 592 days for aminoglutethimide. The relative risk of progression letrozole 2.5: aminoglutethimide was 0.74 (95% CI (0.57, 0.94); P= 0.02)

10. PRESENTATION

Emvia® 2.5 mg is supplied in blister packs of 30 tablets.

11. STORAGE CONDITIONS

Do not store above 25°C.

Store in the original package.

Do not use Emvia® after the expiry date which is stated on the carton.

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.

-Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach and sight of children.

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CC-13-01-036
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Shift to the new Uhlmann machine

Version # 0
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Color: Black Dimensions: 140 x 300 mm
Specs: W/F paper 45g/m²

Approved by /date

Materials Control: _____

Tech mngr: _____

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PHARMACODE
Value: 140
2+2+8+16+16+32+64 value
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6 5 4 3 2 1 0 position