RALOXIFENE HYDROCHLORIDE

LARFEN

60 mg Film Coated Tablet

Selective Estrogen Receptor Modulator

FORMULATION:

Each film coated tablet contains:

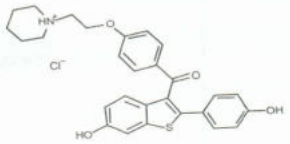
Raloxifene hydrochloride	60mg

Excipients:

Sodium starch glycolate (Primogel) Ph.Eur, Citric acid monohydrate Ph.Eur, Microcrystalline cellulose Ph.Eur, Dibasic Calcium Phosphate Ph.Eur, Poloxamer Ph.Eur, Magnesium stearate Ph.Eur, Opadry White (Titanium dioxide Ph.Eur, Lactose monohydrate Ph.Eur, Macrogol 4000 Ph.Eur, Hypromellose Ph.Eur), Ethanol 96% Ph.Eur, Purified water Ph.Eur

DESCRIPTION:

Raloxifene hydrochloride is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The chemical structure is:



The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride (HCl) has the empirical formula $C_{28}H_{27}NO_4S$ HCl, which corresponds to a molecular weight of 510.05. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

Raloxifene is supplied in a tablet dosage form for oral administration.

MECHANISM OF ACTION:

Decreases in estrogen levels after oophorectomy or menopause lead to increases in bone resorption and accelerated bone loss. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. In addition to loss of estrogen, this imbalance between resorption and formation may be due to age-related impairment of osteoblasts or their precursors. In some women, these changes will eventually lead to decreased bone mass, osteoporosis, and increased risk for fractures, particularly of the spine, hip, and wrist. Vertebral fractures are the most common type of osteoporotic fracture in postmenopausal women.

The biological actions of raloxifene are largely mediated through binding to estrogen receptors. This binding results in activation of certain estrogenic pathways and blockade of others. Thus, raloxifene is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM).

Raloxifene decreases resorption of bone and reduces biochemical markers of bone turnover to the premenopausal range. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, decreases in bone resorption based on radiocalcium kinetics studies, increases in bone mineral density (BMD), and decreases in incidence of fractures.

PHARMACOKINETICS:

Absorption

Raloxifene is absorbed rapidly after oral administration. Approximately 60% of an oral dose is absorbed. Presystemic glucuronidation is extensive. Absolute bioavailability of raloxifene is 2%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Distribution

Raloxifene is distributed extensively in the body. The volume of distribution is not dose dependent. Raloxifene is strongly bound to plasma proteins (98-99%).

Metabolism

Raloxifene undergoes extensive first pass metabolism to the glucuronide conjugates: raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4'-diglucuronide. No other metabolites have been detected. Raloxifene comprises less than 1% of the combined concentrations of raloxifene and the glucuronide metabolites. Raloxifene levels are maintained by enterohepatic recycling, giving a plasma half-life of 27.7 hours.

Results from single oral doses of raloxifene predict multiple dose pharmacokinetics. Increasing doses of raloxifene result in slightly less than proportional increase in the area under the plasma time concentration curve (AUC).

Excretion

The majority of a dose of raloxifene and glucuronide metabolites are excreted within 5 days and are found primarily in the faeces, with less than 6% excreted in urine.

Special populations

Renal insufficiency - Less than 6% of the total dose is eliminated in urine. In a population pharmacokinetic study, a 47% decrease in lean body mass adjusted creatinine clearance resulted in a 17% decrease in raloxifene clearance and a 15% decrease in the clearance of raloxifene conjugates.

Hepatic insufficiency - The pharmacokinetics of a single dose of raloxifene in patients with cirrhosis and mild hepatic impairment (Child-Pugh class A) have been compared to that in healthy individuals. Plasma raloxifene concentrations were approximately 2.5-fold higher than in controls and correlated with bilirubin concentrations.

INDICATION:

Treatment and Prevention of Osteoporosis in Postmenopausal Women

- Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- Must not be used in women with childbearing potential.
- Active or past history of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.
- Hepatic impairment, including cholestasis.
- Severe renal impairment.
- Unexplained uterine bleeding.

Raloxifene should not be used in patients with signs or symptoms of endometrial cancer, as safety in this patient group has not been adequately studied.

DOSAGE AND ADMINISTRATION:

Recommended Dosing

The recommended dosage is one 60 mg raloxifene tablet daily, which may be administered any time of day without regard to meals. No dose adjustment is necessary for the elderly. Due to the nature of this disease process, Raloxifene is intended for long-term use.

Generally, calcium and vitamin D supplements are advised in women with a low dietary intake.

Renal impairment: Raloxifene should not be used in patients with severe renal impairment. In patients with moderate and mild renal impairment, Raloxifene should be used with caution.

Hepatic impairment: Raloxifene should not be used in patients with hepatic impairment.

WARNINGS & PRECAUTIONS:

Cardiovascular Disease

Raloxifene should not be used for the primary or secondary prevention of cardiovascular disease. In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, no cardiovascular benefit was demonstrated after treatment with raloxifene for 5 years.

Venous Thromboembolism

In clinical trials, Raloxifene -treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism). Other venous thromboembolic events also could occur. A less serious event, superficial thrombophlebitis, also has been reported more frequently with Raloxifene. The greatest risk for deep vein thrombosis and pulmonary embolism occurs during the first 4 months of treatment, and the magnitude of risk appears to be similar to the reported risk associated with use of hormone therapy. Because immobilization increases the risk for venous thromboembolic events independent of therapy, Raloxifene should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and Raloxifene therapy should be resumed only after the patient is fully ambulatory. In addition, women taking Raloxifene should be advised to move about periodically during prolonged travel. The risk-benefit balance should be considered in women at risk of thromboembolic disease for other reasons, such as congestive heart failure, superficial thrombophlebitis, and active malignancy.

Death Due to Stroke

In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, an increased risk of death due to stroke was observed after treatment with Raloxifene. During an average follow-up of 5.6 years, 59 (1.2%) Raloxifene -treated women died due to a stroke compared to 39 (0.8%) placebo-treated women (22 versus 15 per 10,000 women-years; hazard ratio 1.49; 95% confidence interval, 1.00- 2.24; $p=0.0499$). There was no statistically significant difference between treatment groups in the incidence of stroke (249 in Raloxifene [4.9%] versus 224 placebo [4.4%]). Raloxifene had no significant effect on all-cause mortality. The risk-benefit balance should be considered in women at risk for stroke, such as prior stroke or transient ischemic attack (TIA), atrial fibrillation, hypertension, or cigarette smoking.

Premenopausal Use

There is no indication for premenopausal use of Raloxifene. Safety of Raloxifene in premenopausal women has not been established and its use is not recommended.

History of Breast Cancer

Raloxifene has not been adequately studied in women with a prior history of breast cancer.

Use in Men

There is no indication for the use of Raloxifene in men. Raloxifene has not been adequately studied in men and its use is not recommended.

Unexplained Uterine Bleeding

Any unexplained uterine bleeding should be investigated as clinically indicated. Raloxifene - treated and placebo-treated groups had similar incidences of endometrial proliferation.

Breast Abnormalities

Any unexplained breast abnormality occurring during Raloxifene therapy should be investigated. Raloxifene does not eliminate the risk of breast cancer.

History of Hypertriglyceridemia when Treated with Estrogens

Limited clinical data suggest that in patients with a history of oral oestrogen-induced hypertriglyceridaemia (>5.6mmol/l), raloxifene may be associated with a marked increase in serum triglycerides. Patients with this medical history should have serum triglycerides monitored when taking raloxifene.

Hepatic Dysfunction

Raloxifene is metabolised primarily in the liver. Single doses of raloxifene given to patients with cirrhosis and mild hepatic impairment (Child-Pugh class A) produced plasma concentrations of raloxifene which were approximately 2.5-times the controls. The increase correlated with total bilirubin concentrations. Until safety and efficacy have been evaluated further in patients with hepatic insufficiency, the use of Raloxifene is not recommended in this patient population. Serum total bilirubin, gamma-glutamyl transferase, alkaline phosphatase, ALT and AST should be closely monitored during treatment if elevated values are observed.

DRUG INTERACTIONS:

Concurrent administration of either calcium carbonate or aluminium and magnesium-hydroxide containing antacids do not affect the systemic exposure of raloxifene. Co-administration of raloxifene and warfarin does not alter the pharmacokinetics of either compound. However, modest decreases in the prothrombin time have been observed, and if raloxifene is given concurrently with warfarin or other coumarin derivatives, the prothrombin time should be monitored. Effects on prothrombin time may develop over several weeks if raloxifene treatment is started in patients who are already on coumarin anticoagulant therapy.

Raloxifene has no effect on the pharmacokinetics of methylprednisolone given as a single dose. Raloxifene does not affect the steady-state AUC of digoxin. The Cmax of digoxin increased by less than 5%.

The influence of concomitant medication on raloxifene plasma concentrations was evaluated in the prevention and treatment trials. Frequently co-administered medicinal products included: paracetamol, non-steroidal anti-inflammatory drugs (such as acetylsalicylic acid, ibuprofen, and naproxen), oral antibiotics, H1-antagonists, H2-antagonists, and benzodiazepines. No clinically relevant effects of the co-administration of the agents on raloxifene plasma concentrations were identified.

Concomitant use of vaginal oestrogen preparations was allowed in the clinical trial programme, if necessary to treat atrophic vaginal symptoms. Compared to placebo there was no increased use in raloxifene-treated patients.

In vitro, raloxifene did not interact with the binding of warfarin, phenytoin, or tamoxifen.

Raloxifene should not be co-administered with cholestyramine (or other anion exchange resins), which significantly reduces the absorption and enterohepatic cycling of raloxifene.

Peak concentrations of raloxifene are reduced with co-administration with ampicillin. However, since the overall extent of absorption and the elimination rate of raloxifene are not affected, raloxifene can be concurrently administered with ampicillin.

Raloxifene modestly increases hormone-binding globulin concentrations, including sex steroid binding globulins (SHBG), thyroxine binding globulin (TBG), and corticosteroid binding globulin (CBG), with corresponding increases in total hormone concentrations. These changes do not affect concentrations of free hormones.

USE IN SPECIFIC POPULATIONS

Pregnancy and lactation

Raloxifene is only for use in postmenopausal women.

Raloxifene must not be taken by women of childbearing potential. Raloxifene may cause foetal harm when administered to a pregnant woman. If this medicinal product is used mistakenly during pregnancy or the patient becomes pregnant while taking it, the patient should be informed of the potential hazard to the foetus.

It is not known whether raloxifene is excreted in human milk. Its clinical use, therefore, cannot be recommended in lactating women. It may affect the development of the baby.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, 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. Based on clinical trials, there is no need for dose adjustment for geriatric patients.

Use in renal impairment

Raloxifene should not be used in patients with severe renal impairment. In patients with moderate and mild renal impairment, Raloxifene should be used with caution.

Use in hepatic impairment

Raloxifene should not be used in patients with hepatic impairment.

Effects on ability to drive and use machines

Raloxifene has no known effect on driving or the ability to use machinery.

ADVERSE REACTIONS:

In osteoporosis treatment and prevention studies involving over 13,000 postmenopausal women, all undesirable reactions were recorded. The duration of treatment in these studies ranged from 6 to 60 months. The majority of undesirable reactions have not usually required cessation of therapy.

In the prevention population, discontinuations of therapy due to any undesirable reaction occurred in 10.7% of 581 raloxifene -treated patients and 11.1% of 584 placebo-treated patients. In the treatment population, discontinuations of therapy due to any clinical adverse experience occurred in 12.8% of 2,557 raloxifene-treated patients and 11.1% of 2,576 placebo-treated patients.

The undesirable reactions associated with the use of raloxifene in osteoporosis clinical trials are summarised in the table below. The following convention has been used for the classification of the adverse reactions: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Vascular disorders *Very common:* Vasodilatation (hot flushes). *Uncommon:* Venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis. Superficial vein thrombophlebitis.
Musculoskeletal and connective tissue disorders *Common:* Leg cramps.
General disorders and administration site conditions *Very common:* Flu syndrome. Common: Peripheral oedema.

Compared with placebo-treated patients, the occurrence of vasodilatation (hot flushes) was modestly increased in raloxifene patients (clinical trials for the prevention of osteoporosis, 2 to 8 years postmenopausal, 24.3% raloxifene and 18.2% placebo; clinical trials for the treatment of osteoporosis, mean age 66, 10.6% for raloxifene and 7.1% placebo). This undesirable reaction was most common in the first 6 months of treatment, and seldom occurred de novo after that time.

In a study of 10,101 postmenopausal women with documented coronary heart disease or at increased risk for coronary events (RUTH), the occurrence of vasodilatation (hot flushes) was 7.8% in the raloxifene-treated patients and 4.7% in the placebo-treated patients.

Across all placebo-controlled clinical trials of raloxifene in osteoporosis, venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis, occurred at a frequency of approximately 0.8% or 3.22 cases per 1,000 patient years. A relative risk of 1.60 (CI 0.95, 2.71) was observed in raloxifene -treated patients compared to placebo. The risk of a thromboembolic event was greatest in the first four months of therapy. Superficial vein thrombophlebitis occurred in a frequency of less than 1%.

In the RUTH study, venous thromboembolic events occurred at a frequency of approximately 2.0% or 3.88 cases per 1,000 patient-years in the raloxifene group and 1.4% or 2.70 cases per 1,000 patient-years in the placebo group. The hazard ratio for all VTE events in the RUTH study was HR = 1.44, (1.06 – 1.95). Superficial vein thrombophlebitis occurred at a frequency of 1% in the raloxifene group and 0.6% in the placebo group.

Another undesirable reaction observed was leg cramps (5.5% for raloxifene, 1.9% for placebo in the prevention population; and 9.2% for raloxifene, 6.0% for placebo in the treatment population).

In the RUTH study, leg cramps were observed in 12.1% of raloxifene-treated patients and 8.3% of placebo-treated patients.

Flu syndrome was reported by 16.2% of raloxifene -treated patients and 14.0% of placebo-treated patients.

One further change was seen which was not statistically significant ($p > 0.05$), but which did show a significant dose trend. This was peripheral oedema, which occurred in the prevention population at an incidence of 3.1% for raloxifene and 1.9% for placebo; and in the treatment population occurred at an incidence of 7.1% for raloxifene and 6.1% for placebo.

In the RUTH study, peripheral oedema occurred in 14.1% of the raloxifene-treated patients and 11.7% of the placebo-treated patients, which was statistically significant.

Slightly decreased (6-10%) platelet counts have been reported during raloxifene treatment in placebo-controlled clinical trials of raloxifene in osteoporosis.

Rare cases of moderate increases in AST and/or ALT have been reported where a causal relationship to raloxifene cannot be excluded. A similar frequency of increases was noted among placebo patients. In a study (RUTH) of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, an additional adverse reaction of cholelithiasis occurred in 3.3% of patients treated with raloxifene and 2.6% of patients treated with placebo. Cholecystectomy rates for raloxifene (2.3%) were not statistically significantly different from placebo (2.0%).

Raloxifene (n=317) was compared with continuous combined (n = 110) hormone replacement therapy (HRT) or cyclic (n = 205) HRT patients in some clinical trials. The incidence of breast symptoms and uterine bleeding in raloxifene treated women was significantly lower than in women treated with either form of HRT.

OVERDOSE:

Adverse reaction were reported in approximately half of the adults who took raloxifene 180mg or more & included leg cramps & dizziness. Two children 18 months of age injected raloxifene 180mg. In these 2 children symptoms reported included ataxia, diarrhea, dizziness, flushing, rash, tremor & vomiting as well as elevation in alkaline phosphates.

Storage Condition:

Store at temperatures not exceeding 30°C, away from direct sunlight.
Keep out of reach of children.

Caution:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:

Transparent PVC/PE/PVDC/Aluminium foil of 4 x 7 film coated Tablets (Box of 28's)

Manufactured by : **PHARMATHEN S.A.**
6, Dervenakion Street, 153 51 Pallini, Attiki, Greece

For : **MEGA LIFESCIENCES (AUSTRALIA) PTY LTD**
60, National Avenue, Pakenham, Victoria 3810, Australia

MEGA We care

Imported & Distributed by: **METRO DRUG, INC.**
Mañalac Avenue, Bagumbayan, Taguig City, Philippines

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

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