Vexiphen®

Raloxifene Hydrochloride

FORMS AND PRESENTATION
Vexiphen®: Film coated tablets: Box of 30.
COMPOSITION:
Vexiphen®: Each film coated tablet contains: Raloxifene Hydrochloride 60 mg.
Excipients: lactose anhydrous, starch, croscarmellose sodium, polyvinyl pyrrolidone, magnesium stearate, crospovidone, colloidal anhydrous silica, hydroxy propyl methyl cellulose, purified talc, titanium dioxide, triacetin.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
As a selective estrogen receptor modulator (SERM), Raloxifene has selective agonist or antagonist activities on tissues responsive to estrogen. It acts as an agonist on bone and partially on cholesterol metabolism (decrease in total and LDL-cholesterol), but not in the hypothalamus or in the uterine or breast tissues.
Raloxifene's biological actions, like those of estrogen, are mediated through high affinity binding to estrogen receptors and regulation of gene expression. This binding results in differential expression of multiple estrogen-regulated genes in different tissues. Recent data suggests that the estrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.
a) Skeletal Effects
The decrease in estrogen availability which occurs at menopause, leads to marked increases in bone resorption, bone loss and risk of fracture. In postmenopausal women with osteoporosis, Raloxifene reduces the incidence of vertebral fractures, preserves bone mass and increases bone mineral density (BMD).
Prevention of osteoporosis with Raloxifene is indicated for women within ten years of menopause, with BMD of the spine between 1.0 and 2.5 SD (Standard Deviation) below the mean value of a normal young population, taking into account their high lifetime risk for osteoporotic fractures. Likewise, Raloxifene is indicated for the treatment of osteoporosis or established osteoporosis in women with BMD of the spine 2.5 SD below the mean value of a normal young population and/or with vertebral fractures, irrespective of BMD.
b) Effects on lipid metabolism and cardiovascular risk
Clinical trials showed that a 60 mg daily dose of Raloxifene significantly decreased total cholesterol (3 to 6 %), and LDL cholesterol (4 to 10 %). Women with the highest baseline cholesterol levels had the greatest decreases. HDL cholesterol and triglyceride concentrations did not change significantly. After 3 years therapy Raloxifene decreased fibrinogen (6.71 %). In the osteoporosis treatment study, significantly fewer Raloxifene-treated patients required initiation of hypolipidaemic therapy compared to placebo.
Raloxifene therapy for 8 years did not significantly affect the risk of cardiovascular events in patients enrolled in the osteoporosis treatment study. Similarly, in the RUTH study (Raloxifene Use for The Heart), Raloxifene did not affect the incidence of myocardial infarction, hospitalized acute coronary syndrome, stroke or overall mortality, including overall cardiovascular mortality, compared to placebo.
The relative risk of venous thromboembolic events observed during Raloxifene treatment was 1.60 (CI 0.95, 2.71) when compared to placebo, and was 1.0 (CI 0.3, 6.2) when compared to estrogen or hormonal replacement therapy. The risk of a thromboembolic event was greatest in the first four months of therapy.
c) Effects on the endometrium and on the pelvic floor
In clinical trials, Raloxifene did not stimulate the postmenopausal uterine endometrium. Compared to placebo, Raloxifene was not associated with spotting or bleeding or endometrial hyperplasia. Nearly 3,000 transvaginal ultrasound (TVUs) examinations were evaluated from 831 women in all dose groups. Raloxifene treated women consistently had an endometrial thickness which was indistinguishable from placebo. After 3 years of treatment, at least a 5 mm increase in endometrial thickness, assessed with transvaginal ultrasound, was observed in 1.9 % of the 211 women treated with Raloxifene 60 mg/day compared to 1.8 % of the 219 women who received placebo. There were no differences between the Raloxifene and placebo groups with respect to the incidence of reported uterine bleeding.
Endometrial biopsies taken after six months therapy with Raloxifene 60 mg daily demonstrated non-proliferative endometrium in all patients. In addition, in a study with 2.5 x the recommended daily dose of Raloxifene there was no evidence of endometrial proliferation and no increase in uterine volume.
In the osteoporosis treatment trial, endometrial thickness was evaluated annually in a subset of the study population (1,644 patients) for 4 years. Endometrial thickness measurements in Raloxifene treated women were not different from baseline after 4 years of therapy. There was no difference between Raloxifene and placebo treated women in the incidences of vaginal bleeding (spotting) or vaginal discharge. Fewer Raloxifene treated women than placebo treated women required surgical intervention for uterine prolapse. Safety information following 3 years of Raloxifene treatment suggests that Raloxifene treatment does not increase pelvic floor relaxation and pelvic floor surgery.
After 4 years, Raloxifene did not increase the risk of endometrial or ovarian cancer. In postmenopausal women who received Raloxifene treatment for 4 years, benign endometrial polyps were reported in 0.9 % compared to 0.3 % in women who received placebo treatment.
d) Effects on breast tissue
Raloxifene does not stimulate breast tissue. Across all placebo-controlled trials, Raloxifene was indistinguishable from placebo with regard to frequency and severity of breast symptoms (no swelling, tenderness and breast pain).
Over the 4 years of the osteoporosis treatment trial (involving 7705 patients), Raloxifene treatment compared to placebo reduced the risk of total breast cancer by 62 % (RR 0.38; CI 0.21, 0.69), the risk of invasive breast cancer by 71 % (RR 0.29, CI 0.13, 0.58) and the risk of invasive estrogen receptor (ER) positive breast cancer by 79 % (RR 0.21, CI 0.07, 0.50). Raloxifene has no effect on the risk of ER negative breast cancers. These observations support the conclusion that Raloxifene has no intrinsic estrogen agonist activity in breast tissue.
e) Effects on cognitive function
No adverse effects on cognitive function have been seen.
Pharmacokinetic Properties
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 hrs. 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 Cl_{cr} 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.
INDICATIONS
Vexiphen® is indicated for the treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.
When determining the choice of Vexiphen® or other therapies, including estrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits.
CONTRAINDICATIONS
- Hypersensitivity to Raloxifene or to any of the excipients.
- Must not be used in women with child bearing 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.

PRECAUTIONS
Raloxifene is associated with an increased risk for venous thromboembolic events that is similar to the reported risk associated with current use of hormone replacement therapy. The risk-benefit balance should be considered in patients at risk of venous thromboembolic events of any etiology. Raloxifene should be discontinued in the event of an illness or a condition leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible in case of the illness, or from 3 days before the immobilisation occurs. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile.
In a study of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, Raloxifene did not affect the incidence of myocardial infarction, hospitalized acute coronary syndrome, overall mortality, including overall cardiovascular mortality, or stroke, compared to placebo. However, there was an increase in death due to stroke in women assigned to Raloxifene. The incidence of stroke mortality was 1.5 per 1000 women per year for placebo versus 2.2 per 1000 women per year for Raloxifene. This finding should be considered when prescribing Raloxifene for postmenopausal women with a history of stroke or other significant stroke risk factors, such as transient ischemic attack or atrial fibrillation.
There is no evidence of endometrial proliferation. Any uterine bleeding during Raloxifene therapy is unexpected and should be fully investigated by a specialist. The two most frequent diagnoses associated with uterine bleeding during Raloxifene treatment were endometrial atrophy and benign endometrial polyps. In postmenopausal women who received Raloxifene treatment for 4 years, benign endometrial polyps were reported in 0.9% compared to 0.3% in women who received placebo treatment.
Raloxifene is metabolized 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

PI018/1

monitored during treatment if elevated values are observed.
Limited clinical data suggest that in patients with a history of oral estrogen-induced hypertriglyceridemia (>5.6 mmol/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.
The safety of Raloxifene in patients with breast cancer has not been adequately studied. No data are available on the concomitant use of Raloxifene and agents used in the treatment of early or advanced breast cancer. Therefore, Raloxifene should be used for osteoporosis treatment and prevention only after the treatment of breast cancer, including adjuvant therapy, has been completed.
As safety information regarding co-administration of Raloxifene with systemic estrogens, is limited, such use is not recommended.
Raloxifene is not effective in reducing vasodilatation (hot flushes), or other symptoms of the menopause associated with estrogen deficiency.
This drug contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PREGNANCY AND LACTATION

Raloxifene is only for use in postmenopausal women.
Raloxifene must not be taken by women of child bearing 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. Raloxifene may affect the development of the baby.

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 C_{max} 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 estrogen 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.

ADVERSE EFFECTS

In osteoporosis treatment and prevention studies involving over 13,000 postmenopausal women all adverse effects were recorded. The duration of treatment in these studies ranged from 6 to 60 months. The majority of adverse effects have not usually required cessation of therapy.
In the prevention population discontinuations of therapy due to any adverse effect 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 adverse effects associated with the use of Raloxifene in osteoporosis clinical trials are summarized below. The following convention has been used for the classification of the adverse effects: 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 adverse effect was most common in the first 6 months of treatment, and seldom occurred again 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 1000 patient-years in the Raloxifene group and 1.4% or 2.70 cases per 1000 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 in a frequency of 1% in the Raloxifene group and 0.6% in the placebo group.
Another adverse effect 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 can not 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.
The adverse effects reported in post-marketing experience are presented below.
Blood and lymphatic system disorders: Very rare: thrombocytopenia.
Gastrointestinal disorders: Very rare: gastrointestinal symptoms such as nausea, vomiting, abdominal pain, dyspepsia.
General disorders and administration site conditions: Rare: peripheral oedema.
Investigations: Very rare: increased blood pressure.
Nervous system disorders: Very rare: headache, including migraine.
Skin and subcutaneous tissue disorders: Very rare: rash.
Reproductive system and breast disorders: Very rare: mild breast symptoms such as pain, enlargement and tenderness.
Vascular disorders: Rare: venous thromboembolic reaction. Very rare: arterial thromboembolic reaction.

DOSAGE AND ADMINISTRATION

The recommended dose is one tablet daily by oral administration, which may be taken at any time of the day without regard to meals. No dose adjustment is necessary for the elderly. Due to the nature of this disease process, Vexiphen® is intended for long term use. Generally calcium and vitamin D supplements are advised in women with a low dietary intake.
Use in renal impairment:
Vexiphen® should not be used in patients with severe renal impairment. In patients with moderate and mild renal impairment, Vexiphen® should be used with caution.
Use in hepatic impairment:
Vexiphen® should not be used in patients with hepatic impairment.

OVERDOSAGE

In some clinical trials, daily doses were given up to 600 mg for 8 weeks and 120 mg, for 3 years. No cases of Raloxifene overdose were reported during clinical trials.
In adults, symptoms of leg cramps and dizziness have been reported in patients who took more than 120 mg as a single ingestion.
In accidental overdose in children younger than 2 years of age, the maximum reported dose has been 180 mg. In children, symptoms of accidental overdose included ataxia, dizziness, vomiting, rash, diarrhea, tremor, and flushing, and elevation in alkaline phosphatase.
The highest overdose has been approximately 1.5 grams. No fatalities associated with overdose have been reported.
There is no specific antidote for Raloxifene hydrochloride.

STORAGE CONDITIONS

Store below 25°C.
Keep in original pack in intact conditions.

Date of revision: October 2010.

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 for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta SAL
Dbayeh- Lebanon