

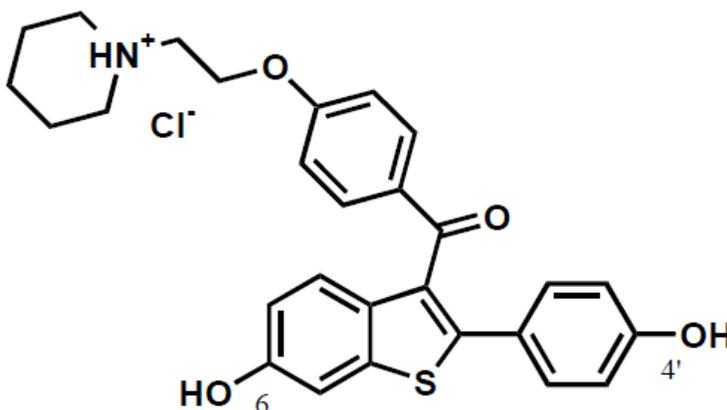
APO-RALOXIFENE TABLETS

NAME OF THE MEDICINE

Raloxifene hydrochloride

Chemical Name: methanone, [6-hydroxy-2-(4-(2-(1-piperidinyloxy)phenoxy)phenyl)benzo[*b*]thien-3-yl]-[4-(2-(1-piperidinyloxy)phenoxy)phenyl]-, hydrochloride

Structural Formula:



Molecular Formula: $C_{28}H_{27}NO_4S.HCl$

Molecular Weight: 510.05

CAS Registry Number: 82640-04-8 (Raloxifene hydrochloride)
84449-90-1 (Raloxifene free base)

DESCRIPTION

Raloxifene hydrochloride is an off-white to pale-yellow solid that is very slightly soluble in water.

In addition to raloxifene hydrochloride, APO-Raloxifene 60 mg tablets also contains lactose, crospovidone, magnesium stearate, silica colloidal anhydrous, hypromellose, hydroxypropylcellulose, macrogol 8000, titanium dioxide and purified water

PHARMACOLOGY

Long term post-menopausal health and the role of oestrogen

Oestrogen exerts agonistic effects on a number of bodily tissues. For example, oestrogen affects the structure and integrity of bone.

Decreases in oestrogen levels after oophorectomy or menopause lead to increases in bone resorption, accelerated bone loss and increased risk of fracture. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. This imbalance between resorption and formation is related to loss of oestrogen, and may also involve age-related impairment of osteoblasts or their precursors. Vertebral fractures are the most common type of osteoporotic fracture in post-menopausal women.

These fractures are associated with substantial morbidity and impairment in quality of life. Managing post menopausal changes that are associated with decreased oestrogen is a challenge. Other conditions not

related to decreased oestrogen levels, such as cancers of the breast and uterus, also increase post-menopause.

Mode of action

Raloxifene has agonistic effects at some oestrogen receptors, antagonistic effects at other oestrogen receptors and has been referred to as a selective oestrogen receptor modulator (SERM). It exerts the positive effects of oestrogen on bone and lipid metabolism, while specifically antagonising some of the potentially negative effects of oestrogen on uterine and breast tissues. The agonistic effect of raloxifene on bone and lipid metabolism has been shown to be dose dependent.

Raloxifene decreases resorption of bone and normalises bone turnover to the pre-menopausal range. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, decreases in bone resorption, increases in bone mineral density (BMD) and decreases in incidences of fractures.

The biological actions of raloxifene, like those of oestrogen, are mediated through binding to oestrogen receptors. This binding results in differential expression of multiple oestrogen-regulated genes in different tissues. Recent data suggest that the oestrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.

Pharmacokinetic properties

In a study comparing raloxifene 60 mg tablets with the innovator, the two products were shown to be bioequivalent. The 90% confidence interval of the relative mean for the log-transformed AUC_t and C_{max} of raloxifene was 0.96% - 1.09% and 0.95% - 1.15% respectively.

Absorption

Raloxifene is absorbed rapidly after oral administration. Although approximately 60% of an oral dose is absorbed, presystemic glucuronide conjugation is extensive and absolute bioavailability is 2.0%. The time to reach average maximum plasma concentration and bioavailability are functions of absorption, 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.

Protein Binding

Approximately 98% to 99% of raloxifene is bound *in vitro* to plasma proteins, including both albumin and α -1-acid glycoprotein. Raloxifene is not displaced *in vitro* by its glucuronide conjugates.

Metabolism

Raloxifene comprises less than 1% of the combined concentrations of Raloxifene and the glucuronide metabolites in plasma. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, prolonging raloxifene's plasma elimination half-life to an average of 27.7 hours after oral dosing.

Results from single oral doses of raloxifene predict multiple dose pharmacokinetics, although increasing doses of raloxifene result in slightly less than a proportional increase in the area under the plasma concentration/time curve.

Excretion

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

Special Populations

Renal Insufficiency - Less than 6% of the total dose is eliminated in urine. In the osteoporosis treatment and prevention trials, blood levels of raloxifene and its metabolite were not affected by renal function in women having estimated creatinine clearance as low as 21 mL/min.

Hepatic Insufficiency - The pharmacokinetics of a single dose of raloxifene in patients with hepatic dysfunction have been compared to that in healthy individuals. Plasma raloxifene concentrations were approximately 2.5-fold higher than in controls and correlated with total bilirubin concentrations.

CLINICAL TRIALS

Clinical data indicate that raloxifene, a selective oestrogen receptor modulator (SERM), has oestrogen-like effects on bone (increase in BMD) and on lipid (decrease in total and LDL cholesterol levels) metabolism. Preclinical data in rodents suggest that raloxifene is an oestrogen antagonist in uterine and breast tissues. Clinical data demonstrate that raloxifene lacks oestrogen-like effects on uterus and breast tissue.

Skeletal effects

In post-menopausal women with osteoporosis, raloxifene reduces the risk of vertebral fractures. Raloxifene also increases BMD of the spine, hip and total body. Similarly, in post-menopausal women without osteoporosis, raloxifene preserves bone mass and significantly increases BMD of the hip and spine.

i) Treatment of osteoporosis. The effects of raloxifene on fracture incidence and BMD in post-menopausal women with osteoporosis were examined at 3 years in a large randomized placebo-controlled, double-blind osteoporosis treatment trial. The study population consisted of 7705 post-menopausal women with osteoporosis as defined by: a) low BMD (vertebral or hip BMD at least 2.5 standard deviations below the mean value for healthy young women) without baseline vertebral fractures, or b) one or more baseline vertebral fractures. Women enrolled in this study had a median age of 67 years (range 31 to 80) and a median time since menopause of 19 years. All women received calcium (500 mg/day) and vitamin D (400-600 IU/day).

Raloxifene hydrochloride, 60 mg administered once daily, increased spine and hip BMD by 2-3% and total body and ultradistal radius BMD by 1-2%, and decreased the incidence of one or more vertebral fractures by as much as 55% (Table 1) compared to an active therapy of calcium plus vitamin D supplemented placebo. Raloxifene reduced the incidence of vertebral fractures whether or not patients had experienced a previous fracture.

Table 1: Effect of Raloxifene Hydrochloride 60 mg on Risk of Vertebral Fractures

	Number of Patients		Relative Risk
	Raloxifene	Placebo	(95% CI)
Patients with no baseline fracture ^a	n=1401	n=1457	
Number of patients with ≥1 new vertebral fractures	27	62	0.45 (0.29, 0.71)
Patients with ≥1 baseline fracture ^a	n=858	n=835	
Number of patients with ≥1 new vertebral fractures	121	169	0.70 (0.56, 0.86)
All randomised patients	n=2557	n=2576	
Number of patients with ≥1 new clinical (painful) vertebral fractures	47	81	0.59 (0.41, 0.83)

^a - includes all patients with baseline and at least one follow-up radiograph

ii) Prevention of osteoporosis. The effects of raloxifene on BMD in post-menopausal women were examined in three large randomised, placebo-controlled, double-blind osteoporosis prevention trials: (1) a North American trial enrolled 544 women; (2) a European trial, 601 women; and (3) an international trial, 619 women who had undergone hysterectomy. In these trials, all women received calcium supplementation (400 to 600 mg/day). Women enrolled in these studies had a median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years post-menopause). The majority of the women were Caucasian (93.5%). Women were included if they had spine bone mineral density between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women. The mean T scores (number of standard deviations above or below the mean in healthy young women) ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD.

Raloxifene produced significant increases in bone density of the hip (1.3% to 2.4%) and spine (1.8% to 2.4%) compared to placebo (Table 2). Raloxifene also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's Triangle (hip) by 3.1% to 4.0%. The effects of raloxifene on forearm BMD were inconsistent between studies.

Table 2: Raloxifene hydrochloride (60 mg once daily) related increases in BMD for the three osteoporosis prevention studies expressed as mean percentage increase versus calcium-supplemented placebo at 24 months^a

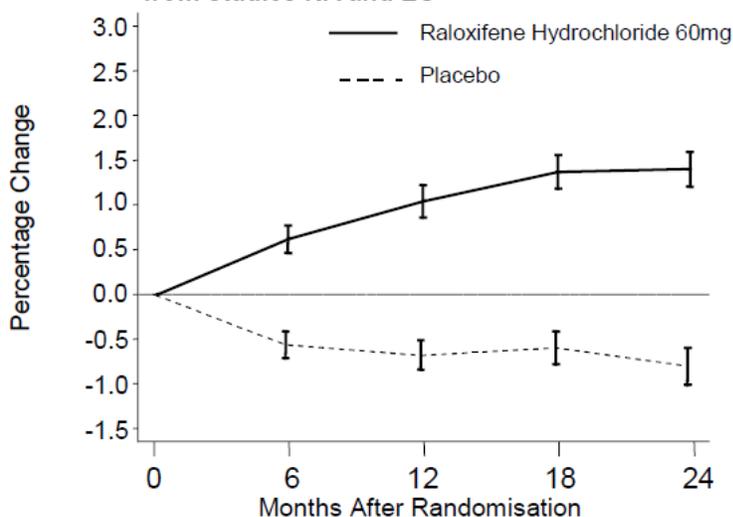
Site	Study		
	NA %	EU %	INT ^b %
Total Hip	2.0	2.4	1.3
Femoral Neck	2.1	2.5	1.6
Trochanter	2.2	2.7	1.3
Intertrochanter	2.3	2.4	1.3
Lumbar Spine	2.0	2.4	1.8

Abbreviations: NA = North America, EU = European, INT = International

^a - Intent-to-treat analysis; last observation carried forward.

^b - All women in the study had previously undergone hysterectomy.

Fig 1. Total hip mean percentage change from baseline – All placebo and raloxifene subjects 24-month-data from studies NA and EU^a



^a - Intent-to-treat analysis; last observation carried forward.

iii) Calcium kinetics. Raloxifene and oestrogen affect bone remodelling and calcium metabolism similarly. In a 31-week open-label radiocalcium kinetics study, 33 early postmenopausal women were randomised to treatment with once-daily raloxifene hydrochloride 60 mg, cyclic oestrogen/progestin (HRT) or no treatment. Raloxifene was associated with reduced bone resorption and a mean positive shift in calcium balance of 60 mg per day, due primarily to decreased urinary calcium losses. These findings were similar to those observed with HRT.

iv) Histomorphometry (bone quality). In the osteoporosis treatment study, bone biopsies for qualitative and quantitative histomorphometry were obtained at baseline and after 2 years of treatment with placebo, raloxifene hydrochloride 60-mg or raloxifene hydrochloride 120-mg daily. There were 56 paired biopsies evaluable (24 placebo, 20 raloxifene hydrochloride 60-mg and 12 raloxifene hydrochloride 120-mg). Similarly to placebo-treated patients, in raloxifene-treated patients, normal bone quality was maintained; specifically, there was no evidence of osteomalacia, marrow fibrosis, cellular toxicity or woven bone after 2 years of treatment.

The effects of raloxifene on bone histomorphometry were determined by pre-and post-treatment biopsies in a 6-month study of Caucasian post-menopausal women who received once-daily doses of raloxifene 60 mg or 0.625 mg conjugated oestrogens. Ten raloxifenetreated and 8 oestrogen-treated women had evaluable bone biopsies at baseline and after 6 months of therapy. Bone in raloxifene treated and oestrogen-treated women showed no evidence of mineralisation defects, woven bone or marrow fibrosis.

Effects on the endometrium

In clinical trials, raloxifene did not stimulate the post-menopausal 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. Furthermore, 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 of therapy with raloxifene demonstrated nonproliferative endometrium in all patients. In addition, in a study with 2.5 times 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 (1781 patients) for three years. Placebo-treated women had a 0.27 mm mean decrease from baseline in endometrial thickness over 3 years, whereas the raloxifene hydrochloride 60-mg-treated women had a 0.06 mm mean increase (not different from baseline).

After three years, raloxifene did not increase the risk of endometrial or ovarian cancer.

Effects on breast tissue

Preclinical data in rodents suggest that raloxifene is an oestrogen antagonist in uterine and breast tissues. Across all placebo-controlled trials, raloxifene was indistinguishable from placebo with regard to frequency and severity of breast symptoms. Raloxifene was associated with significantly fewer breast symptoms (swelling, tenderness, breast pain) than reported by patients receiving oestrogens, with or without added progestins.

MORE Trial

The effect of raloxifene was assessed in a randomised, placebo-controlled, double-blind, multinational osteoporosis treatment trial in postmenopausal women. Table 3 presents efficacy and selected safety outcomes.

Table 3: Raloxifene (60 mg Once Daily) vs. Placebo on Outcomes in Postmenopausal Women with Osteoporosis

Outcomes	Placebo (n=2576)		Raloxifene (n=2557)		HR (95% CI) ^a
	n	IR ^a	n	IR ^a	
Clinical vertebral fractures	107	12.27	62	7.08	0.57 (0.14, 2.47)
Death	36	4.13	23	2.63	0.63 (0.38, 1.07)
Death due to stroke	6	0.69	3	0.34	0.49 (0.12, 1.98)
Stroke	56	6.42	43	4.91	0.76 (0.51, 1.14)
Deep vein thrombosis	8	0.92	20	2.28	2.50 (1.10, 5.68)
Pulmonary embolism	4	0.46	11	1.26	2.76 (0.88, 8.67)

Endometrial and uterine cancer ^b	5	0.74	5	0.74	1.01 (0.29, 3.49)
Ovarian cancer	6	0.69	3	0.34	0.49 (0.12, 1.95)
Hot flushes	151	17.31	237	27.06	1.61 (1.31, 1.97)
Peripheral oedema	134	15.36	164	18.73	1.23 (0.98, 1.54)
Cholelithiasis	45	5.16	53	6.05	1.18 (0.79, 1.75)

^a - Abbreviations: CI = confidence interval; HR = hazard ratio; IR = annual incidence rate per 1000 women

^b - Only patients with an intact uterus were included (MORE: placebo = 1999, raloxifene = 1950).

INDICATIONS

APO- Chemmart Terry White Chemists Raloxifene is indicated for:

- The prevention and treatment of osteoporosis in post-menopausal women.

CONTRAINDICATIONS

Raloxifene is contraindicated in women who are or may become pregnant. Raloxifene may cause fetal harm when administered to a pregnant woman. Raloxifene is not indicated for premenopausal women. Safety of raloxifene in premenopausal women has not been established and its use is not recommended.

Raloxifene is contraindicated in women with active or a past history of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.

Raloxifene is also contraindicated in women with hypersensitivity to raloxifene or other ingredients in the tablet.

Raloxifene is contraindicated for use in males. It is only for use in post-menopausal women.

PRECAUTIONS

In a multi-centre double-blind, placebo-controlled, randomised, parallel study of 10,101 postmenopausal women with documented coronary heart disease or at increased risk for coronary events followed for a median of 5.6 years, there was an increased risk of mortality due to stroke in the group taking raloxifene, although the incidence of stroke, myocardial infarction, hospitalised acute coronary syndrome, cardiovascular mortality, or overall mortality was comparable to placebo. 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. The risk-benefit balance of raloxifene for treatment or prevention of osteoporosis in postmenopausal women with a history of stroke or other significant stroke risk factors, such as transient ischaemic attack or atrial fibrillation, should be considered when prescribing raloxifene.

Raloxifene is associated with an increased risk for venous thromboembolic events that appears to be 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 VTEs (venous thromboembolic events) of any aetiology. Raloxifene should be discontinued in the event of a condition or illness leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible with illness, or from three days before prolonged immobilisation is likely. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. In addition, women taking raloxifene should be advised to move about periodically during prolonged travel.

Raloxifene is not effective in reducing vasodilatation (hot flushes) associated with oestrogen deficiency.

Raloxifene is metabolised primarily in the liver. Single doses of raloxifene given to patients with cirrhosis 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.

The concurrent use of raloxifene and systemic oestrogen for hormone replacement therapy (HRT) has not been studied systematically. Therefore, raloxifene should not be used concomitantly with systemic oestrogens.

Raloxifene has not been associated with endometrial proliferation (see CLINICAL TRIALS, Effects on the endometrium). Unexplained uterine bleeding should be considered abnormal and investigated as clinically indicated.

In patients with a history of oral oestrogen-induced hypertriglyceridaemia (>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.

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

Effects on Fertility

Reproductive effects observed in animal studies are consistent with the known pharmacological profile of raloxifene. Oestrous cycling was disrupted in mice given dietary doses ≥ 15 mg/kg/day, and in rats at oral gavage doses ≥ 1 mg/kg/day, with a no-effect dose level of 0.1 mg/kg/day in the latter study. Fertility of female rats was abolished at dietary doses ≥ 5 mg/kg/day (no-effect dose not established). In one study, fertility of female rats dosed by oral gavage at 10 mg/kg/day was almost completely restored immediately after cessation of treatment and was completely restored after a 2-week recovery period. However, disruption of oestrous cycling and infertility persisted up to 5 weeks in a few rats dosed at 6-63 mg/kg/day in a dietary study. In rats becoming pregnant immediately after cessation of treatment at 10 mg/kg/day by oral gavage, litter size was reduced, gestation length was slightly increased and the timing of events in neonatal development was slightly altered; similar effects were not seen in animals mated after a 2-week recovery period. When given by oral gavage to mated female rats during the pre-implantation period at 0.1 to 10 mg/kg/day, raloxifene delayed and disrupted embryo implantation resulting in prolonged gestation, and reduced litter size. Development of offspring to weaning was not affected. The reproductive effects of raloxifene in animal studies reflect the pharmacological activity of the drug and similar effects may occur if raloxifene is administered to pre-menopausal women.

Raloxifene is a potent antioestrogen in the rat uterus and prevented growth of oestrogen-dependent mammary tumours in rats and mice.

Use in Pregnancy - Pregnancy Category X¹

Raloxifene is only for use in post-menopausal women.

Raloxifene must not be taken by women of child bearing potential. Animal studies showed that raloxifene caused foetal malformations in rabbits and abnormalities in the reproductive system and impaired reproductive function in the female offspring of rats. These developmental effects were observed at pharmacologically active dose levels and similar effects on foetal development may occur if raloxifene is administered to a pregnant woman. If this drug is used mistakenly during pregnancy or the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the foetus.

Use in Lactation

It is not known whether raloxifene is excreted in human or animal milk. In animal studies, oral administration of raloxifene (0.1 to 10 mg/kg/day) during pregnancy and lactation caused suppression of pup growth during lactation and histopathological changes in the reproductive system of female offspring; fertility of female offspring was impaired at the high dose level. Raloxifene's use, therefore, cannot be recommended in lactating women, as it may affect the development of the baby.

Carcinogenicity

In a 2-year carcinogenicity study in rats, an increase in ovarian tumours of granulosa/theca cell origin was observed in females given a dietary dose of 279 mg/kg/day (approximately 400 times the AUC in humans). In a 21-month dietary study in mice, there was an increased incidence of testicular interstitial cell tumours and prostatic adenomas and adenocarcinomas in males given 41 to 210 mg/kg/day

¹ Category X - Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

(comparable to 4.7 to 24 times the AUC in humans) and prostatic leiomyoblastoma in males given 210 mg/kg/day. An increased incidence of ovarian tumours in female mice given dietary doses of 9 to 242 mg/kg/day (comparable to 0.3 to 34 times the AUC in humans) included benign and malignant tumours of granulosa/theca cell origin and benign tumours of epithelial cell origin. The female rodents in these studies were treated during their reproductive lives, when their ovaries were functional and highly responsive to hormonal stimulation.

Genotoxicity

Raloxifene was not genotoxic in assays of gene mutation, chromosomal damage, DNA damage or sister chromatid exchange.

INTERACTIONS WITH OTHER MEDICINES

Cholestyramine

Raloxifene should not be co-administered with cholestyramine or other anion exchange resins. The absorption and enterohepatic cycling of raloxifene is significantly reduced by cholestyramine.

Ampicillin and other oral antimicrobials

Peak concentrations of raloxifene are reduced by co-administration with ampicillin. This reduction is consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, as the overall extent of absorption and the elimination rate of raloxifene are not affected, raloxifene can be concurrently administered with ampicillin. In the osteoporosis treatment trial, co-administered oral antimicrobial agents (including amoxicillin, cephalexin, ciprofloxacin, macrolide antibiotics, sulfamethoxazole/trimethoprim and tetracycline) had no effect on plasma raloxifene concentration.

Corticosteroids

The chronic administration of raloxifene in post-menopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose.

Digoxin

Raloxifene has no effect on the pharmacokinetics of digoxin. In the osteoporosis treatment trial, co-administered digoxin had no effect on plasma raloxifene concentration.

Gastrointestinal Medications

Concurrent administration of either calcium carbonate or aluminium and magnesium-hydroxide containing antacids does not alter the initial absorption or systemic exposure (AUC_{0-t}) of raloxifene. In the osteoporosis treatment trial, coadministered gastrointestinal medications (including bisacodyl, cisapride, docusate, H₂- antagonists, laxatives, loperamide, omeprazole and psyllium) had no effect on plasma raloxifene concentration.

Highly glucuronidated drugs

The influence of co-administered highly glucuronidated drugs (including paracetamol, ketoprofen, morphine and oxazepam) on raloxifene plasma concentrations was evaluated in the osteoporosis treatment trial. No clinically significant effects of these agents on raloxifene plasma concentrations were identified.

Highly protein-bound drugs

The influence of co-administered highly protein-bound drugs (including diazepam, gemfibrozil, ibuprofen, naproxen and warfarin) on raloxifene plasma concentrations was evaluated in the osteoporosis treatment trial. No clinically significant effects of these agents on raloxifene plasma concentrations were identified. In vitro, raloxifene did not affect the binding of phenytoin, tamoxifen or warfarin. As small decreases in the prothrombin time have been observed with raloxifene, if raloxifene is given concurrently with warfarin or other coumarin derivatives, the prothrombin time should be monitored.

Hormones

Raloxifene 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.

Lipid-lowering drugs

Raloxifene lowers serum total and LDL cholesterol but does not affect serum concentrations of total HDL cholesterol or triglycerides. These effects should be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidaemia. Concurrent use of raloxifene and lipid-lowering agents has not been studied.

Concomitant use of oestrogens

In the clinical trial program, there were no interactions noted with concomitant use of vaginal oestrogen preparations and raloxifene (see PRECAUTIONS).

ADVERSE EFFECTS

Osteoporosis Treatment Clinical Trial

Therapy was discontinued due to an adverse event in 10.9% of women treated with raloxifene hydrochloride 60 mg and 8.8% of women treated with placebo. Common adverse reactions considered to be related to raloxifene therapy were hot flushes and leg cramps. Hot flushes were most commonly reported during the first 6 months of treatment and were not different from placebo thereafter.

Osteoporosis Prevention Clinical Trial

The adverse event most frequently reported as the reason for discontinuation in patients treated with raloxifene was hot flushes. Discontinuation rates due to hot flushes did not differ significantly between raloxifene and placebo groups (1.7% and 2.2%, respectively).

Osteoporosis Treatment and Prevention Clinical Trials

Across all placebo-controlled clinical trials of raloxifene in osteoporosis, venous thromboembolic events, including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis occurred in a frequency of approximately 0.7 % or 3.25 cases per 1,000 patient years. A relative risk of 2.32 (CI 1.26, 4.26) 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%.

Table 4 lists adverse events occurring in either the osteoporosis treatment or the prevention placebo-controlled clinical trial databases at a frequency $\geq 2.0\%$ in either group and in more raloxifene-treated women than in placebo-treated women. Adverse events are shown without attribution of causality.

Table 4: Adverse events occurring in placebo-controlled osteoporosis clinical trials at a frequency $\geq 2.0\%$ and in more raloxifene hydrochloride-treated (60 mg once daily) women than placebo-treated women

Body System	Treatment		Prevention	
	Raloxifene N=2557 %	Placebo N=2576 %	Raloxifene N=581 %	Placebo N=584 %
<i>Body as a Whole</i>				
Infection	A	A	15.1	14.6
Flu syndrome	13.5	11.4	14.6	13.5
Headache	9.2	8.5	A	A
Leg Cramps	7.0	3.7	5.9	1.9
Chest Pain	A	A	4.0	3.6
Fever	3.9	3.8	3.1	2.6
<i>Cardiovascular System</i>				
Hot Flushes	9.7	6.4	24.6	18.3
Migraine	A	A	2.4	2.1
Syncope	2.3	2.1	B	B
Varicose Vein	2.2	1.5	B	B
<i>Digestive System</i>				
Nausea	8.3	7.8	8.8	8.6
Diarrhoea	7.2	6.9	A	A

Dyspepsia	A	A	5.9	5.8
Vomiting	4.8	4.3	3.4	3.3
Flatulence	A	A	3.1	2.4
Gastrointestinal Disorder	A	A	3.3	2.1
Gastroenteritis	B	B	2.6	2.1
<i>Metabolic and Nutritional</i>				
Weight Gain	A	A	8.8	6.8
Peripheral Oedema	5.2	4.4	3.3	1.9
<i>Musculoskeletal System</i>				
Arthralgia	15.5	14.0	10.7	10.1
Myalgia	A	A	7.7	6.2
Arthritis	A	A	4.0	3.6
Tendon Disorder	3.6	3.1	A	A
<i>Nervous System</i>				
Depression	A	A	6.4	6.0
Insomnia	A	A	5.2	4.3
Vertigo	4.1	3.7	A	A
Neuralgia	2.4	1.9	B	B
Hypaesthesia	2.1	2.0	B	B
<i>Respiratory System</i>				
Sinusitis	7.9	7.5	10.3	6.5
Rhinitis	10.2	10.1	A	A
Bronchitis	9.5	8.6	A	A
Pharyngitis	5.3	5.1	7.6	7.2
Cough Increased	9.3	9.2	6.0	5.7
Pneumonia	A	A	2.6	1.5
Laryngitis	B	B	2.2	1.4
<i>Skin and Appendages</i>				
Rash	A	A	5.5	1.7
Sweating	2.5	2.0	3.1	
<i>Special Senses</i>				
Conjunctivitis	2.2	1.7	B	B
<i>Urogenital System</i>				
Vaginitis	A	A	4.3	3.6
Urinary Tract Infection	A	A	4.0	3.9
Cystitis	4.6	4.5	3.3	3.1
Leukorrhoea	A	A	3.3	1.7
Uterine Disorder ^{a,b}	2.5	1.8	A	A
Endometrial Disorder ^a	B	B	3.1	1.9
Vaginal Haemorrhage	2.5	2.4	A	A
Urinary Tract Disorder	2.5	2.1	A	A

A - Placebo incidence greater than or equal to raloxifene hydrochloride 60 mg incidence

B - Less than 2% incidence and more frequent with raloxifene hydrochloride 60 mg

^a - Treatment-emergent uterine-related adverse event, including only patients with an intact uterus:

Prevention Trials: raloxifene hydrochloride 60 mg, n=354, Placebo, n=364; Treatment Trial: raloxifene hydrochloride 60 mg, n=1948, Placebo, n=1999.

^b - Actual terms most frequently referred to endometrial fluid.

Comparison of Raloxifene Hydrochloride 60 mg and Hormone Replacement Therapy Raloxifene hydrochloride 60 mg was compared with oestrogen-progestin replacement therapy (HRT) in 3 clinical trials for prevention of osteoporosis. Table 5 shows adverse events occurring more frequently in one treatment group and at an incidence $\geq 2.0\%$ in any group. Adverse events are shown without attribution of causality.

Table 5: Adverse events reported in the clinical trials for osteoporosis prevention with raloxifene hydrochloride (60 mg once daily) and continuous combined or cyclic oestrogen plus progestin (HRT) at an incidence $\geq 2.0\%$ in any treatment group^a

Adverse Event	Raloxifene (N=317) %	HRT - Continuous Combined (N=96) %	HRT - Cyclic (N=219) %
<i>Urogenital System</i>			
Breast Pain	4.4	37.5	29.7
Vaginal Bleeding ^b	6.2	64.2	88.5
<i>Digestive</i>			
Flatulence	1.6	12.5	6.4
<i>Cardiovascular</i>			
Hot Flushes	28.7	3.1	5.9
<i>Body as a Whole</i>			
Infection	11.0	0	6.8
Abdominal Pain	6.6	10.4	18.7
Chest pain	2.8	0	0.5

^a - These data are from both blinded and open-label studies.

^b - Treatment-emergent uterine-related adverse event, including only patients with an intact uterus: raloxifene hydrochloride 60 mg, n=290, HRT-Continuous Combined, n=67, HRT-Cyclic, n=217.

Continuous Combined HRT = 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate. Cyclic HRT = 0.625 mg conjugated oestrogens for 28 days with concomitant 5 mg medroxyprogesterone acetate or 0.15 mg norgestrel on days 1 through 14 or 17 through 28.

Breast Pain

Across all placebo-controlled trials, raloxifene was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. Raloxifene was associated with less breast pain and tenderness than reported by women receiving estrogens with or without added progestin.

Gynaecologic Cancers

Raloxifene-treated and placebo-treated groups had similar incidences of endometrial cancer and ovarian cancer.

Safety

The safety of raloxifene (60 mg once daily) was assessed in a placebo-controlled multinational trial of 10,101 postmenopausal women (age range 55–92) with documented coronary heart disease (CHD) or multiple CHD risk factors. Median study drug exposure was 5.1 years for both treatment groups. Therapy was discontinued due to an adverse reaction in 25% of 5044 raloxifene-treated women and 24% of 5057 placebo treated women. The incidence per year of all-cause mortality was similar between the raloxifene (2.07%) and placebo (2.25%) groups.

Adverse reactions reported more frequently in raloxifene-treated women than in placebo-treated women included peripheral oedema (14.1% raloxifene versus 11.7% placebo), muscle spasms/leg cramps (12.1% raloxifene versus 8.3% placebo), hot flushes (7.8% raloxifene versus 4.7% placebo), venous thromboembolic events (2.0% raloxifene versus 1.4% placebo), and cholelithiasis (3.3% raloxifene versus 2.6% placebo).

Post-Marketing Experience

In addition to the above, the following adverse events have been reported during post-marketing experience for raloxifene:

- Anxiety
- Bone pain
- Pain in extremity
- Musculoskeletal pain

DOSAGE AND ADMINISTRATION

The recommended dosage is one 60 mg tablet per day orally, which may be taken at any time of day without regard to meals. No dose adjustment is necessary for the elderly.

Supplemental calcium should be added to the diet if daily intake is inadequate.

There are no data on the discontinuation effects of raloxifene. Raloxifene exerts its effect through the oestrogen receptor and does not accumulate in any target tissue. Therefore, continuous daily treatment with raloxifene is required to maintain the effect of the drug.

Concomitant use of oestrogens – see PRECAUTIONS.

OVERDOSAGE

In clinical trials, no overdose of raloxifene has been reported. In an 8-week study of 63 postmenopausal women, a dose of raloxifene hydrochloride of 600 mg/day was safely tolerated. In clinical trials, more than 2500 post-menopausal women received a daily dose of 120 mg for three years.

In postmarketing spontaneous reports, overdose has been reported very rarely (less than 1 out of 10000 [$<0.01\%$] patients treated). The highest overdose has been approximately 1.5 grams. No fatalities associated with overdose have been reported. In adults, symptoms reported in patients who took more than 120 mg as a single ingestion included leg cramps and dizziness. In some cases, no adverse events were reported as a result of the overdose.

Raloxifene is not indicated for use in children, however, in accidental overdose in children under 2 years of age, the maximum reported dose has been 180mg. In children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhoea, tremor and flushing, as well as elevation in alkaline phosphatase.

No mortality was seen after a single oral dose in rats or mice at 5000 mg/kg (810 times the human dose for rats and 405 times the human dose for mice based on surface area, mg/m^2) or in monkeys at 1000 mg/kg (80 times the AUC in humans).

There is no specific antidote for raloxifene.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

APO-Raloxifene 60 mg Tablets: White, oval, biconvex, film-coated tablet, engraved “APO” on one side, “RAL60” on the other side.

Blister packs of 7 and 28 tablets: AUST R 184797

Bottles of 7, 28, 100 and 500 tablets: AUST R 184794

Not all strengths, pack types and/or pack sizes may be available

APO-Raloxifene is intended for oral administration. Each tablet contains 60 mg of raloxifene hydrochloride as the active ingredient.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 30 March 2012

Date of most recent amendment: 31 May 2012