PRODUCT MONOGRAPH

Pr APO-RALOXIFENE

Raloxifene Hydrochloride Tablets

60 mg

Selective Estrogen Receptor Modulator

APOTEX INC.
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Control #098000

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[Pr]APO- RALOXIFENE
60 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 60 mg	Lactose. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

APO-RALOXIFENE (raloxifene hydrochloride) is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

For either osteoporosis treatment or prevention, supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate.

Postmenopausal osteoporosis may be diagnosed by history or radiographic documentation of osteoporotic fracture, bone mineral densitometry, or physical signs of vertebral crush fractures (e.g., height loss, dorsal kyphosis). Women with diagnosed postmenopausal osteoporosis should be considered for pharmacologic therapy, in conjunction with education and appropriate lifestyle modifications.

No single clinical finding or test result can quantify risk of postmenopausal osteoporosis with certainty. However, clinical assessment can help to identify women at increased risk. Widely accepted risk factors include Caucasian or Asian descent, slender body build, early estrogen deficiency, smoking, alcohol consumption, low calcium diet, sedentary lifestyle, personal history of any fracture after age 40 and family history of osteoporosis. Evidence of increased bone turnover from serum and urine markers and low bone mass (e.g. at least 1 standard deviation below the mean for healthy, young adult women) as determined by densitometric techniques are also predictive. The greater the number of clinical risk factors, the greater the probability of developing postmenopausal osteoporosis. These risk factors may be considered in the decision to use APO-RALOXIFENE for prevention of postmenopausal osteoporosis.

CONTRAINDICATIONS

APO-RALOXIFENE (raloxifene hydrochloride) is contraindicated in women of childbearing potential. APO-RALOXIFENE therapy during pregnancy may be associated with an increased risk of congenital defects in the fetus.

APO-RALOXIFENE is contraindicated in women with active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.

APO-RALOXIFENE is contraindicated in women known to be hypersensitive to raloxifene or other constituents of the tablets.

For a complete listing see the Dosage Forms, composition and Packaging section of the PM.

WARNINGS AND PRECAUTIONS

Venous Thromboembolic Events (VTE)

In clinical trials, raloxifene treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism). The risk of VTE is reported infrequently, occuring in 1.44, 3.32 and 3.63 events per 1,000 person-years for placebo, raloxifene 60 mg/day and raloxifene 120 mg/day, respectively. Other venous thromboembolic events could also 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 is similar to that associated with use of hormone replacement 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. The risk-benefit balance should be considered in women at risk of thromboembolic disease for other reasons.

Premenopausal Use

There is no indication for premenopausal use of APO-RALOXIFENE (raloxifene hydrochloride). Safety of APO-RALOXIFENE in premenopausal women has not been established and its use is not recommended (see CONTRAINDICATIONS).

Hepatic Dysfunction

Raloxifene was studied, as a single dose, in Child-Pugh Class A patients with cirrhosis and serum total bilirubin ranging from 0.6 to 2.0 mg/dL (10.3 to 34.2 mmol/L). Plasma raloxifene concentrations were approximately 2.5 times higher than in controls and correlated with total bilirubin concentrations. Safety and efficacy have not been evaluated further in patients with hepatic insufficiency.

PRECAUTIONS

General

Concurrent Estrogen Therapy: The concurrent use of APO-RALOXIFENE (raloxifene hydrochloride) and systemic estrogen or hormone replacement therapy (ERT or HRT) has not been studied in prospective clinical trials.

Lipid Metabolism: APO-RALOXIFENE lowers serum total and LDL cholesterol by 6% to 11%, but does not affect serum concentrations of total HDL cholesterol or triglycerides. HDL-2 cholesterol subfraction is increased by raloxifene. These effects should be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidemia. Concurrent use of APO-RALOXIFENE and lipid lowering agents has not been studied.

Endometrium: APO-RALOXIFENE does not cause endometrial proliferation (see ACTION AND CLINICAL PHARMACOLOGY and ADVERSE REACTIONS). Unexplained uterine bleeding should be investigated as clinically indicated.

Breast: APO-RALOXIFENE is not associated with breast enlargement, breast pain, or increased risk of breast cancer (see ACTION AND CLINICAL PHARMACOLOGY and ADVERSE REACTIONS). Any unexplained breast abnormality occurring during APO-RALOXIFENE therapy should be investigated.

History of Breast Cancer: APO-RALOXIFENE has not been studied in women with a prior history of breast cancer.

Cognition and Affect: APO-RALOXIFENE has not been associated with deterioration of cognitive function or a change in affect. Any such change during APO-RALOXIFENE use is unlikely to be related to therapy, and should be investigated as clinically indicated.

Estrogen-Induced Hypertriglyceridemia

In a 12 patient, single-arm, open-label study in patients with a history of oral estrogen-induced marked hypertriglyceridemia (generally 5.6 to 39 mmol/L [500 to 3400 mg/dL]), 3 patients had increases of serum triglycerides to >11.3 mmol/L (1000 mg/dL) within 2 weeks after initiation of raloxifene therapy. In 2 of these 3 patients, serum triglyceride levels decreased while raloxifene was continued. Patients with this medical history should have serum triglycerides monitored when taking raloxifene.

Information for Patients

For safe and effective use of APO-RALOXIFENE, the physician should inform patients about the following:

Patient Immobilization: APO-RALOXIFENE should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g. post surgical recovery, prolonged bed rest) and APO-RALOXIFENE therapy should be resumed only after the patient is fully ambulatory because of the increased risk of venous thromboembolic events.

Vasodilatation: APO-RALOXIFENE is not effective in reducing vasodilatation (hot flashes or flushes) associated with estrogen deficiency. In some patients, vasodilatation may occur upon beginning APO-RALOXIFENE therapy.

Other Osteoporosis Treatment and Prevention Measures: Patients should be instructed to take supplemental calcium and/or vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking, and/or alcohol consumption, if these factors exist.

Special Population

Use in Men

There is no indication for use of APO-RALOXIFENE in men.

Pediatric Use

APO-RALOXIFENE should not be used in pediatric patients. The safety and efficacy of raloxifene has not been studied in pediatric populations.

Geriatric Use

In the osteoporosis treatment trial of 7705 postmenopausal women, 4621 women were considered geriatric (greater than 65 years old). Of these, 845 women were greater than 75 years old. Safety and efficacy in older and younger postmenopausal women in the osteoporosis treatment trial appear to be comparable.

Pregnancy

Raloxifene should not be used in women who are or may become pregnant (See Contraindications).

Nursing Mothers

Raloxifene should not be used by lactating women (See Contraindications). It is not known whether raloxifene is excreted in human milk.

ADVERSE REACTIONS

The safety of raloxifene has been established in Phase 2 and Phase 3 placebo-controlled, estrogen-controlled, and HRT-controlled studies. Twelve studies comprised the primary safety database for the prevention indication, and the safety of raloxifene in the treatment of osteoporosis was assessed in a large (N=7705), multinational, placebo-controlled trial. In the osteoporosis prevention trials, the duration of treatment ranged from 2 to 30 months and 2036 women were exposed to raloxifene. In the osteoporosis treatment trial, 5129 women were exposed to raloxifene (2557 received 60 mg/day and 2572 received 120 mg/day) for 36 months. In the 4th year, patients were permitted the concomitant use of bisphosphonates, calcitonin and fluorides. All events were reported irrespective of causality.

Because clinical trials are conducted under very specific conditions the adverse drug reactions rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from the clinical trials is useful in identifying drug-related adverse vents and for approximating rates.

Commonly Observed Adverse Events

The most commonly observed treatment-emergent adverse events associated with the use of raloxifene in double-blind, placebo-controlled, osteoporosis treatment and prevention clinical trials that occurred at an incidence ≥2% are shown in Table 1. These events occurred in postmenopausal women who took raloxifene for up to 36 months in the osteoporosis treatment trial and for up to 30 months in the osteoporosis prevention trials. The differences between raloxifene and placebo treatments were significant at $p<0.05$.

Table 1 Adverse Events Associated with Use of Raloxifene (60 mg once daily) Occurring at a Frequency Greater than in Placebo-Treated Patients and at an Incidence ≥2.0% in Either Group

	Treatment		Prevention	
Adverse Event	Raloxifene (N=2557) %	Placebo (N=2576) %	Raloxifene (N=581) %	Placebo (N=584) %
Vasodilatation	9.7	6.4	24.6	18.3
Leg Cramps	7.0	3.7	5.9	1.9

Vasodilatation events (hot flashes or flushes) were common in placebo-treated women, and the frequency was modestly increased in raloxifene-treated women. The first occurrence of this event was most commonly reported during the first 6 months of treatment and infrequently was reported *de novo* after that time. At 48 months in the osteoporosis treatment trial, vasodilation was reported in 10.6% of patients on raloxifene versus 7.1% of placebo patients ($p<0.001$), and leg cramps were reported in 9.2% of patients on raloxifene versus 6.0% of placebo patients ($p<0.001$).

At 48 months in the same osteoporosis treatment trial, flu syndrome (16.2% of raloxifene treated patients versus 14.0% of placebo patients), uterine disorder (endometrial cavity fluid in 12.7% of raloxifene treated patients versus 9.6% of placebo patients) and peripheral edema (7.1% of raloxifene treated patients versus 6.1% of placebo patients) were also treatment-emergent adverse events (frequency > 2%), which occurred more frequently with patients receiving raloxifene compared to placebo ($p<0.05$).

Adverse Events Associated with Discontinuation of Therapy

The majority of adverse events occurring during clinical trials have been mild and have not required discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 10.9% of 2557 raloxifene-treated women and 8.8% of 2576 placebo-treated women in the osteoporosis treatment trial, and in 11.4% of 581 raloxifene-treated women and 12.2% of 584 placebo-treated women in the osteoporosis prevention trials.

Adverse Events in Placebo-Controlled Clinical Trials

Table 2 lists adverse events occurring in either the osteoporosis treatment (up to 3 years) or prevention placebo-controlled clinical trials with raloxifene at a frequency ≥2.0% in either group and at rates in raloxifene-treated women numerically greater than in placebo-treated women. Events previously discussed are not included in this table. Only one of the differences shown in the table (flu syndrome) was statistically significant and no causal inferences can be made for any of these adverse events.

Table 2 Adverse Events Occurring in Placebo-Controlled Osteoporosis Clinical Trials (up to 36 months) at a Frequency ≥2.0% in Either Group and at Rates in Raloxifene-Treated (60 mg once daily) Women Numerically Greater Than in Placebo-Treated Women

	Treatment		Prevention	
Body System	**Raloxifene (N=2557) %**	**Placebo (N=2576) %**	**Raloxifene (N=581) %**	**Placebo (N=584) %**
Body as a Whole				
Infection	A	A	15.1	14.6
Flu Syndrome	13.5[a]	11.4	14.6	13.5
Headache	9.2	8.5	A	A
Chest Pain	A	A	4.0	3.6
Fever	3.9	3.8	3.1	2.6
Cardiovascular				
Migraine	A	A	2.4	2.1
Syncope	2.3	2.1	B	B
Varicose Vein	2.2	1.5	B	B
Digestive				
Nausea	8.3	7.8	8.8	8.6
Diarrhea	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
Metabolic and Nutritional				
Weight Gain	A	A	8.8	6.8
Peripheral Edemar	5.2[b]	4.4	3.3[b]	1.9

Body System	Treatment		Prevention	
	Raloxifene (N=2557) %	Placebo (N=2576) %	Raloxifene (N=581) %	Placebo (N=584) %
Musculoskeletal				
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
Nervous				
Depression	A	A	6.4	6.0
Insomnia	A	A	5.5	4.3
Vertigo	4.1	3.7	A	A
Neuralgia	2.4	1.9	B	B
Hypesthesia	2.1	2.0	B	B
Respiratory				
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
Skin and Appendages				
Rash	A	A	5.5	3.8
Sweating	2.5	2.0	3.1	1.7
Special Sinses				
Conjunctivitis	2.2	1.7	B	B

Body System	Treatment		Prevention	
	Raloxifene (N=2557) %	Placebo (N=2576) %	Raloxifene (N=581) %	Placebo (N=584) %
Urogenital				
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
Leukorrhea	A	A	3.3	1.7
Uterine Disorder[c,d]	2.5	1.8	A	A
Endometrial Disorder[c]	B	B	3.1	1.9
Vaginal Hemorrhage	2.5	2.4	A	A
Urinary Tract Disorder	2.5	2.1	A	A

A Placebo incidence greater than or equal to raloxifene incidence.
B Less than 2% incidence and more frequent with raloxifene.
[a] Significantly ($p<0.05$) different from placebo.
[b] Significant dose trends at $p<0.05$
[c] Treatment-emergent uterine-related adverse event, including only patients with an intact uterus: Treatment Trial: Raloxifene n=1948, Placebo n=1999; Prevention Trials: Raloxifine n=354, Placebo n=364.
[d] Actual terms most frequently referred to endometrial fluid.

The incidence trend of treatment-emergent adverse events (frequency ≥2%) after year 4 of the osteoporosis treatment trial were generally similar to the 1 to 3 year results presented in Table 9. However, the following table (Table 3) details the treatment-emergent adverse events where the relative incidences changed between raloxifene treated patients and placebo patients (e.g. reversed). Please note that in the final (4^{th}) year of the study, patients were permitted the concomitant use of bisphosphonates, fluorides and calcitonins.

Table 3 Changes in Adverse Events from the 3^{rd} Year to the 4^{th} Year Occurring in a Placebo-Controlled Osteoporosis Treatment Clinical Trial at a Frequency ≥2.0% in Either Raloxifene-Treated (60 mg once daily) Women or Placebo-Treated Women at 48 Months.

Body System	4^{th} Year Treatment		1^{st} to 3^{rd} Year Incidence Trend (from Table 8)
	Raloxifene (N=2557) %	Placebo (N=2576) %	
Body as a Whole			
Infection	18.2	18.0	A
Chest Pain	8.3	8.0	A
Fever	A	A	C
Cardiovascular			
Syncope	A	A	C

Body System	4th Year Treatment		1st to 3rd Year Incidence Trend (from Table 8)
	Raloxifene (N=2557) %	Placebo (N=2576) %	
Digestive			
Gastroenteritis	2.1	2.0	B
Metabolic and Nutritional			
Weight Gain	3.5	3.4	A
Nervous			
Vertigo	A	A	C
Hypesthesia	A	A	C
Respiratory			
Rhinitis	A	A	C
Pharyngitis	A	A	C

Only those adverse events that changed incidence trend from the 3rd to the 4th year are listed.
A Placebo incidence greater than or equal to raloxifene incidence.
B Less than 2% incidence and more frequent with raloxifene.
C Raloxifene incidence greater than placebo.

Comparison of Raloxifene and Hormone Replacement Therapy Adverse Events

Raloxifene was compared with estrogen-progestin replacement therapy (HRT) in 3 clinical trials for prevention of osteoporosis. Table 4 shows adverse events occurring at an incidence ≥2.0% in any group.

Table 4 Adverse Events Reported In Osteoporosis Prevention Clinical Trials With Raloxifene (60 mg once daily) and Continuous Combined or Cyclic Estrogen Plus Progestin (HRT) at an Incidence ≥2.0% In Any Treatment Group

Adverse Event	Raloxifene N=317 %	HRT-Continuous Combined N=96 %	HRT-Cyclic N=219 %
Urogenital			
Breast Pain	4.4	37.5[a]	29.7[a]
Vaginal Bleeding[C]	6.2	64.2[a]	88.5[a]
Digestive			
Flatulence	1.6	12.5[a]	6.4[a]
Cardiovascular			
Vasodilatation	28.7[b]	3.1	5.9

Adverse Event	Raloxifene N=317 %	HRT-Continuous Combined N=96 %	HRT-Cyclic N=219 %
Body as a Whole			
Infection	11.0[b]	0	6.8
Abdominal Pain	6.6	10.4[a]	18.7[a]
Chest Pain	2.8[b]	0	0.5

[a] Significantly greater in specific HRT group than raloxifene ($p<0.05$)
[b] Significant greater in raloxifene than in HRT ($p<0.05$)
[c] Treatment-emergent uterine-related adverse events, excluding patients who had a hysterectomy. (Raloxifene n=290, HRT-Continuous Combined n=67; HRT-Cyclic n=217)

Continuous Combined HRT = 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate

Cyclic HRT = 0.625 mg conjugated equine estrogen for 28 days with concomitant 5 mg medroxyprogesterone acetate or 0.15 mg norgestrel on Days 1 through 14 or 17 through 28.

Additional Safety Information

Endometrium: All cases of endometrial carcinoma are reviewed without knowledge of treatment status (blinded) by an independent Adjudication Review Board. Raloxifene does not increase the risk of endometrial cancer when compared to placebo. Raloxifene does not increase the risk of breast cancer when compared to placebo.

Breast: All cases of breast cancer in women enrolled in clinical trials are reviewed without knowledge of treatment status (blinded) by an independent Adjudication Review Board. A statistically significant 56% reduction (95% confidence interval, 31 % to 73% reduction) has been observed in the incidence of newly-diagnosed breast cancer in raloxifene-treated women compared with placebo. The incidence rate of breast cancer was 3.97 per 1000 subject-years for the women receiving placebo and 1.65 per 1000 subject-years for those receiving raloxifene. The long-term effectiveness of raloxifene in reducing the risk of breast cancer has not been fully established. Raloxifene does not increase the risk of breast cancer when compared to placebo.

Ovary: APO-RALOXIFENE does not increase the risk of ovarian carcinoma.

Laboratory Changes: The following changes in analyte concentrations are commonly observed during APO-RALOXIFENE therapy: increased serum HDL-2 cholesterol subfraction and apolipoprotein A1; and reduced serum total cholesterol, LDL cholesterol, fibrinogen, apolipoprotein B, and lipoprotein (a). APO-RALOXIFENE modestly increases hormone-binding globulin concentrations, including sex steroid binding globulin, thyroxine binding globulin, and corticosteroid binding globulin with corresponding increases in measured total hormone concentrations. There is no evidence that these changes in hormone binding globulin concentrations affect concentrations of the corresponding free hormones.

Glycemic Control: Diabetes mellitus was reported more frequently as an adverse event among raloxifene-treated patients (1.2%) compared with placebo-treated patients (0.5%) in the osteoporosis treatment trial. However, there were no differences between the raloxifene and placebo groups in either fasting glucose or hemoglobin A_{1c} (objective measures of glycemic control) in the osteoporosis treatment trial. The diabetes mellitus adverse event finding may have been due to the lower prevalence of diabetes among patients assigned to placebo.

Cardiovascular: Raloxifene has been shown in a double-blind, randomized, placebo-controlled, 6-month trial in 390 postmenopausal women to have no significant effect on C-reactive protein, in contrast to continuous combined hormone replacement therapy, which significantly increased C-reactive protein levels.

C-reactive protein is an independent risk factor for cardiovascular disease; however it remains to be determined how the effects on C-reactive protein influence cardiovascular outcomes in postmenopausal women.

Results from a 6-month placebo-controlled clinical trial involving 390 postmenopausal women receiving hormone replacement therapy (HRT) or raloxifene or placebo, demonstrated that raloxifene (60 mg/day) and HRT had comparable effects on lowering non HDL cholesterol and apo-B/apo-A1 ratio, particularly in women with hypercholsterolemia. Both non-HDL cholesterol and apo-B/apo-Al are clinical markers of serum atherogenicity.

Analysis of 3 year data from 2 double-blind, randomized, placebo-controlled trials involving a total of 1145 healthy postmenopausal women assigned to one of four treatment groups, placebo, raloxifene at doses of 30 mg/day, 60 mg/day or 150 mg/day, showed that raloxifene treatment of 60 mg/day significantly decreased serum and total LDL-C compared to placebo ($p<0.001$) and baseline ($p<0.001$). In the same patient population, HDL-C and triglyceride concentrations remained unchanged from baseline after 3 years of raloxifene treatment for all doses.

In a large 3-year randomized, placebo-controlled, multicentred osteoporosis treatment trial that was extended to a 4th year, there were no significant differences between treatment groups in the overall cohort in the number of combined coronary and cerebrovascular events: 96 (3.7%) with placebo, 82 (3.2%) with 60 mg/day of raloxifene, and 94 (3.7%) with 120 mg/day raloxifene. Relative risks (RRs) were 0.86 (95% CI 0.64-1.15) and 0.98 (95% CI 0.74-1.30) for 60 mg/day and 120 mg/day of raloxifene respectively. Among the subset of 1,035 women with increased baseline CV risk, those assigned to raloxifene had a significantly lower risk of CV events compared to placebo (RR, 0.60; 95% CI, 0.38-0.95 for both raloxifene groups).

In a large 3 year randomized, placebo-controlled, multi-centered osteoporosis treatment trial that was extended to a 4th year, there were no significant differences between treatment groups in the overall cohort in the number of combined coronary and cerebrovascular events: 96 (3.7%) with placebo, 82 (3.2%) with 60 mg/day of raloxifene, and 94 (3.7%) with 120 mg/day raloxifene.

Central Nervous System: In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, cognitive function was assessed as a secondary outcome in 7705 postmenopausal women with osteoporosis. Treatment with raloxifene at 60 mg/day or 120 mg/day for a 3 year period did not affect overall cognitive scores compared to placebo. In the same study, including a 1-year extension during which concomitant medications (bisphosphonates, calcitonins and fluorides) were permitted, neuropsychomotor tests showed no statistically significant differences between placebo and treatment groups for the 4 year period.

DRUG INTERACTIONS

Clinically significant drug-drug interactions are discussed in PRECAUTIONS.

Ampicillin and Other Oral Antimicrobials: Peak concentrations of raloxifene are reduced with coadministration of ampicillin. The reduction in peak concentrations is consistent with reduced enterohepatic cycling associated with antibiotic reduction of enteric bacteria. Since 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 concentrations.

Corticosteroids: The chronic administration of raloxifene in postmenopausal 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, coadministered digoxin had no effect on plasma raloxifene concentration.

Gastrointestinal Medications: Concurrent administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene. In the osteoporosis treatment trial, coadministered gastrointestinal medications (including bisacodyl, cisapride, docusate, H_2-antagonists, laxatives, loperamide, omeprazole and psyllium) had no effect on plasma raloxifene concentration.

Highly Protein-Bound Drugs: Raloxifene is more than 95% bound to plasma proteins. 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.

Highly Glucuronidated Drugs: Raloxifene undergoes extensive first-pass metabolism to glucuronide conjugates. The influence of co-administered highly glucuronidated drugs (including acetaminophen, 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.

Other Medications: The influence of concomitant medications on raloxifene plasma concentrations was evaluated in the osteoporosis treatment clinical trial. The 152 most commonly co-administered medications were grouped by pharmacological class based on their therapeutic use. Frequently co-administered drugs included: ACE inhibitors and angiotensin antagonists, alpha agonists and antagonists, anticholinergics, antidepressants, antimicrobials, antipsychotics, benzodiazepines, beta blockers and agonists, bisphosphonates, calcium channel blockers, diuretics, estrogen preparations, glucocorticoids, guaifenesin, H_1-antagonists, H_2-antagonists and proton pump inhibitors, hypoglycemics, hypolipidemics, iron preparations, muscle relaxants, nitrates, non-benzodiazepine hypnotics, non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, theophylline and thyroid hormone. No clinically relevant effects of the co-administration of any of these agents on raloxifene plasma concentrations were observed.

Cholestyramine: Cholestyramine, an anion exchange resin, significantly reduces the absorption and enterohepatic cycling of raloxifene and should not be coadministered with raloxifene. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect.

Warfarin: Coadministration of raloxifene and warfarin does not alter the pharmacokinetics of either compound. However, modest decreases in prothrombin time have been observed in single-dose studies. If raloxifene is given concurrently with warfarin or other coumarin derivatives, prothrombin time should be monitored.

Drug-food reactions
APO-RALOXIFENE can be administered without regard to meals.

Laboratory Test interactions
APO-RALOXIFENE is not known to interfere with any common laboratory assays (see ADVERSE REACTIONS for additional laboratory safety information).

Pregnancy
APO-RALOXIFENE should not be used in women who are or may become pregnant (see CONTRAINDICATIONS).

Labour and Delivery
APO-RALOXIFENE has no recognized use during labour or delivery.

Nursing Mothers
APO-RALOXIFENE should not be used by lactating women (see CONTRAINDICATIONS). It is not known whether raloxifene is excreted in human milk.

DOSAGE AND ADMINISTRATION

The recommended dosage is one 60-mg APO-RALOXIFENE tablet daily, which may be administered any time of day without regard to meals.

OVERDOSAGE

Incidents of overdose in humans have not been reported. In an 8-week study of 63 postmenopausal women, a dose of raloxifene HCl 600 mg/day was safely tolerated. No mortality was seen after a single oral dose in rats or mice at 5000 mg/kg or in monkeys at 1000 mg/kg. There is no specific antidote for raloxifene.

ACTION AND CLINICAL PHARMACOLOGY

APO-RALOXIFENE (raloxifene hydrochloride) is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The SERM profile of raloxifene includes estrogen agonist effects on bone and lipid metabolism but not in uterine or breast tissues.

Pharmacokinetics

The disposition of raloxifene has been evaluated in more than 3000 postmenopausal women in selected raloxifene osteoporosis treatment and prevention clinical trials using a population approach. Pharmacokinetic data were also obtained in conventional clinical pharmacology studies in 292 postmenopausal women. Raloxifene exhibits high within-subject variability (approximately 30%) of most pharmacokinetic parameters. Table 5 summarizes the pharmacokinetic parameters of raloxifene.

Table 5 Summary of Raloxifene Pharmacokinetic Parameters in the Healthy Postmenopausal Woman

	Cmax[a] (ng/mL)/ (mg/kg)	t½ (hr)	$AUC_{0-\infty}$[a] (ng●hr/mL)/ (mg/kg)	CL/F (L/kg●hr)/	V/F (L/kg)
Single Dose					
Mean	0.50	27.7	27.2	44.1	2348
CV (%)	52	10.7 to 273[b]	44	46	52
Multiple Dose					
Mean	1.36	32.5	24.2	47.4	2853
CV (%)	37	15.8 to 86.6[b]	36	41	56

Abbreviations:

Cmax = maximum plasma concentration, t½ = half-life, AUC = area under the curve, CL = clearance, V = volume of distribution, F = bioavailability, CV = coefficient of variation.

[a] data normalized based on dose in mg and body weight in kg

[b] range of observed half-life

Absorption
Raloxifene is absorbed rapidly after oral administration. Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is 2.0%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene slightly, but does not lead to clinically meaningful changes in systemic exposure. APO-RALOXIFENE can be administered without regard to meals.

Distribution
Following oral administration of single doses ranging from 30 to 150 mg of raloxifene HCl, the apparent volume of distribution is 2348 L/kg and is not dose dependent.

Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins. Raloxifene binds to both albumin and α1-acid glycoprotein, but not to sex steroid binding globulin.

Metabolism
Biotransformation and disposition of raloxifene in humans have been determined following oral administration of ^{14}C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: raloxitene-4'-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4'-diglucuronide. No other metabolites have been detected, providing strong evidence that raloxifene is not metabolized by cytochrome P450 pathways. Unconjugated raloxifene comprises less than 1% of the total radiolabeled material in plasma. The terminal log-linear portion of the plasma concentration curve for raloxifene and the glucuronides are generally parallel. This is consistent with interconversion of raloxifene and the glucuronide metabolites.

Following intravenous administration, raloxifene is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/kg•hr. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life to 27.7 hours after oral dosing.

Results from single oral doses of raloxifene predict multiple-dose pharmacokinetics. Following chronic dosing, clearance ranges from 40 to 60 L/kg•hr. Increasing doses of raloxifene HCl (ranging from 30 to 150 mg) result in slightly less than a proportional increase in the area under the plasma time concentration curve (AUC).

Excretion
Raloxifene is primarily excreted in feces, and negligible amounts are excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates.

Special Populations
Geriatric: The pharmacokinetics of raloxifene are independent of age (42 to 84 years).

Pediatric: The pharmacokinetics of raloxifene have not been evaluated in a pediatric population.

Gender: Total extent of exposure and oral clearance, normalized for lean body weight, are not significantly different between age-matched male and female volunteers.

Race: Pharmacokinetic differences due to race have been studied in 1712 women including 97.5% Caucasian, 1.0% Asian, 0.7% Hispanic, and 0.5% Black in the osteoporosis treatment trial and in 1053 women including 93.5% Caucasian, 4.3% Hispanic, 1.2% Asian, and 0.5% Black in the osteoporosis prevention trials. There were no discernible differences in raloxifene plasma concentrations among these groups. The influence of race can not be conclusively determined because of the small numbers of non-Caucasians.

Renal Insufficiency: Since negligible amounts of raloxifene are eliminated in urine, a study in patients with renal insufficiency was not conducted. In the osteoporosis treatment and prevention trials, raloxifene and metabolite concentrations were not affected by renal function in women having estimated creatinine clearance as low as 21 mL/min (0.35 mL/s).

Hepatic Dysfunction: Raloxifene was studied, as a single dose, in Child-Pugh Class A patients with cirrhosis and total serum bilirubin ranging from 0.6 to 2.0 mg/dL (10.3 to 34.2 μmol/L). Plasma raloxifene concentrations were approximately 2.5 times higher than in controls and correlated with bilirubin concentrations. Safety and efficacy have not been evaluated further in patients with hepatic insufficiency (see WARNINGS).

Pharmacodynamics

General

Postmenopausal women have an increased risk of chronic illnesses such as osteoporosis and atherosclerotic cardiovascular disease resulting from estrogen deficiency. Estrogen replacement reduces the risk of osteoporosis and may reduce the risk of coronary artery disease, but it also increases the risk of endometrial carcinoma and possibly breast cancer. The selective estrogen receptor modulator (SERM) profile of raloxifene includes estrogen agonist effects on bone and lipid metabolism, and estrogen antagonist effects in uterine and breast tissues. Thus, raloxifene is a first line option for the treatment and prevention of postmenopausal osteoporosis.

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 suggest that the estrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.

Effects On the Skeleton

During early to middle adult life, bone undergoes continuous remodeling. In this process, local areas of bone resorption are refilled completely by ensuing bone formation; that is, resorption and formation are in balance. The result is that bone mass remains relatively constant. Ovarian estrogen is important for maintenance of this balance in bone turnover. Marked decreases in estrogen availability, such as after oophorectomy or menopause, lead to marked increases in bone resorption, accelerated bone loss and increased risk of fracture. After menopause, bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses.

This imbalance between resorption and formation may be related to loss of estrogen, or to age-related impairment of osteoblasts or their precursors.

Estrogen replacement therapy reduces resorption of bone by inhibiting the formation and action of osteoclasts, and decreases overall bone turnover. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, histologic evidence of decreased bone resorption and formation, and increased bone mineral density (BMD). Although raloxifene increases BMD to a lesser extent than estrogen, the effects of raloxifene on bone turnover in postmenopausal women parallel those of estrogen, as shown by studies of bone mineral densitometry, radiocalcium kinetics, bone markers, and bone histomorphometry.

Treatment of Osteoporosis: The effects of raloxifene on fracture incidence and BMD in postmenopausal women with osteoporosis were examined at 3 years in a large, randomized, placebo-controlled, double-blind multinational osteoporosis treatment trial. The study population consisted of 7705 postmenopausal women with osteoporosis as defined by: a) low BMD (vertebral or hip bone mineral density 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, 60 mg administered once daily, decreased the incidence of one or more vertebral fractures by as much as 55% (Table 6) and increased BMD 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. The decrease in incidence of vertebral fracture was greater than could be accounted for by increase in BMD alone (Figure 1).

Table 6 Effect of Raloxifene 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 fracture	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 fracture	121	169	0.70 (0.56, 0.86)
All randomised patients	n=2557	n=2576	
Number of patients with ≥ 1 new clinical (painful) vertebral fracture	47	81	0.59 (0.41, 0.83)

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

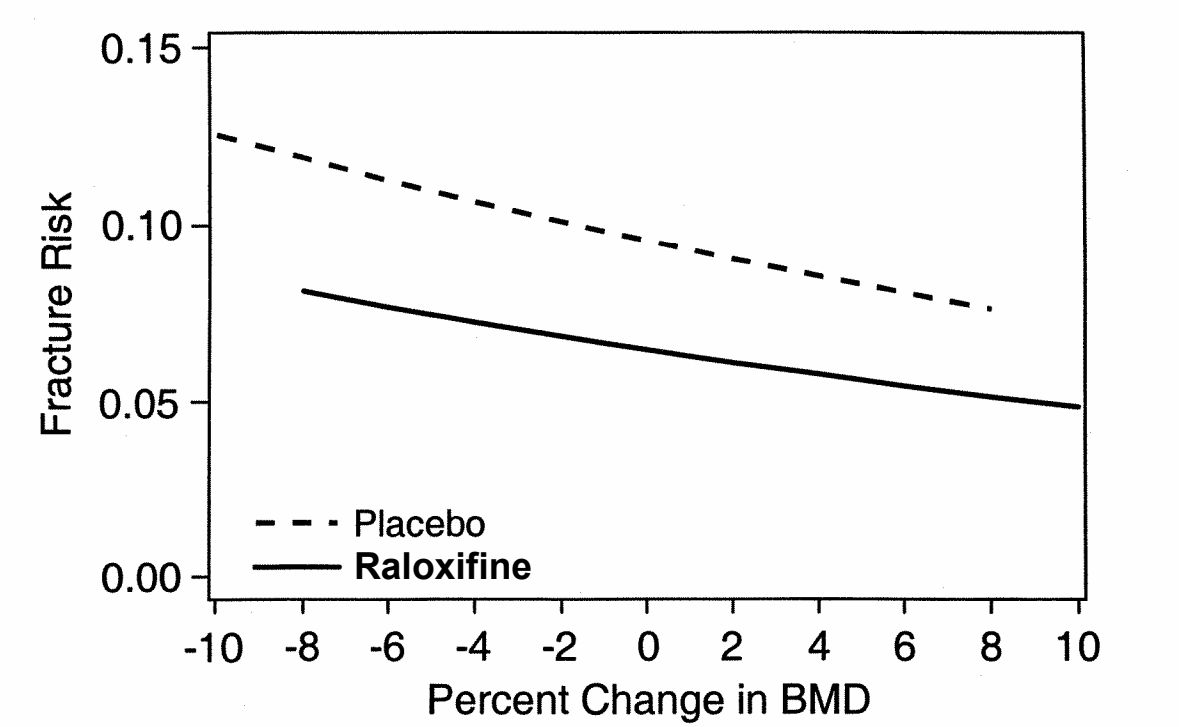


Figure 1 **Changes in BMD do not fully account for vertebral fracture risk reduction. This figure shows the correlation between vertebral fracture risk and percent change in femoral neck BMD at 3 years based on a logistic regression analysis of the clinical trial data. For any given change in BMD from baseline, raloxifene-treated patients had a lower risk for vertebral fracture compared to placebo.**

Retrospective analysis of the patients in the osteoporosis treatment study, demonstrates that there was a statistically significant reduction ($p<0.001$) in the risk of clinical (symptomatic) vertebral fracture after 12 months of treatment. At 12 months the risk of clinical vertebral fractures was decreased by 68% (95% CI, 0.13-0.79) in postmenopausal women taking raloxifene 60 mg per day.

The same osteoporosis treatment study was extended by 12 months to a 4th year during which, patients were permitted the use of concomitant medications, including bisphosphonates, calcitonins and fluorides. The statistically significant reduction in vertebral fractures and increase in BMD seen at 3 years continued into the 4th year extension of the osteoporosis treatment study. The sustained reduction in vertebral fractures is illustrated in Figure 2 below, a Kaplan-Meier analysis of time to first vertebral fracture over the 48 months of the study.

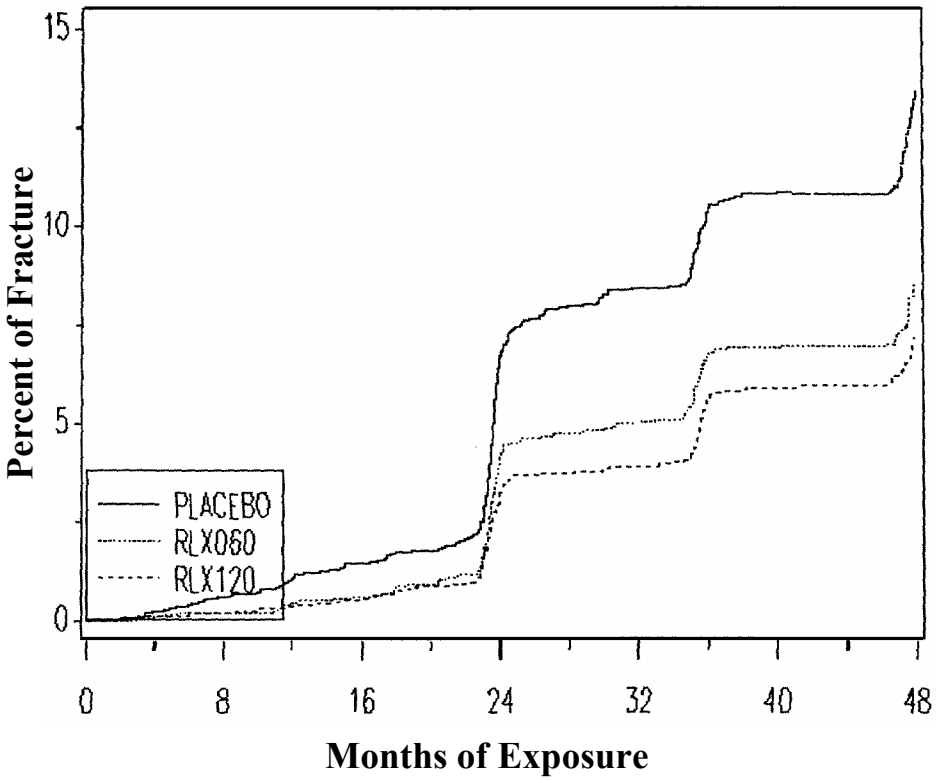


Figure 2 Time to Event for Vertebral Fractures Over 48 Months

Overall osteoporotic fracture risk was significantly reduced with raloxifine therapy. Over 4 years there was no difference seen in nonvertebral fracture incidence in women treated with raloxifene compared to placebo. At 3 years, the risk of individual nonvertebral fractures versus placebo decreased with increasing exposure to raloxifine.

At every time point, the mean percentage change in BMD from baseline for raloxifene was significantly greater than for placebo at each skeletal site measured (Table 7).

Table 7 Raloxifene (60 mg once daily) related increases in BMD for the osteoporosis treatment study expressed as mean percentage increase versus calcium- and vitamin D-supptemented placebo[a]

	Time		
Site	12 Months %	24 Months %	36 Months %
Lumbar Spine	2.0	2.6	2.6
Femoral Neck	1.3	1.9	2.1
Ultradistal Radius	ND	2.2	ND
Distal Radius	ND	0.9	ND
Total Body	ND	1.1	ND

Note: all BMD increases were statistically significant ($p<0.001$)

[a] Intent-to-treat analysis; last observation carried forward

ND = not done (total body and radius BMD were measured only at 24 months)

Discontinuation from the study was required when excessive bone loss or multiple incident vertebral fractures occurred. Such discontinuation was significantly more frequent in the calcium- and vitamin D-supplemented placebo group (3.9%) than in the raloxifene group (1.1 %).

Prevention of Osteoporosis: The effects of raloxifene on BMD in postmenopausal women were examined in three large randomized, 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). Raloxifene, 60 mg raloxifene HCl administered once daily, produced significant increases in bone mass versus calcium supplementation alone, as reflected by dual-energy x-ray absorptiometric (DXA) measurements of hip, spine, and total body BMD. The increases in BMD were statistically significant at 12 months and were maintained at 24 months (Table 8). In contrast, the calcium-supplemented placebo groups lost approximately 1% of BMD over 24 months.

Table 8 Raloxifene Increases in BMD For the Three Osteoporosis Prevention Studies Expressed as Percentage Increase Versus Calcium-Supplemented Placebo at 24 Months

	Study		
Site	N/A %	EU %	INT[a] %
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: N/A = North American, EU = European, INT = International

[a] All women in the study had previously undergone hysterectomy

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%. In the international trial, conjugated equine estrogen 0.625 mg/day (ERT) was used as an active comparator. The mean increases in BMD at 24 months for estrogen compared with placebo were: lumbar spine 5.4%; total hip 2.9%.

Thus, in postmenopausal women, raloxifene preserves bone mass and increases BMD significantly relative to calcium alone at 24 months. The effect on hip bone mass is similar to that for the spine.

Assessments of Bone Turnover: In a 31-week radiocalcium kinetics study, raloxifene was associated with reduced bone resorption and a positive shift in calcium balance (+60 mg Ca/day), due primarily to decreased urinary calcium losses. These findings were similar to those observed with hormone replacement therapy.

In both the osteoporosis treatment and prevention trials, raloxifene therapy resulted in consistent, statistically significant suppression of bone resorption, bone formation, and overall bone turnover, as reflected by changes in serum and urine markers of bone turnover (eg, bone-specific alkaline phosphatase, osteocalcin, and collagen breakdown products). The suppression of bone turnover markers was evident by 3 months and persisted throughout the 36-month and 24-month observation periods, respectively.

Bone Histomorphometry: In the treatment study, bone biopsies for qualitative and quantitative histomorphometry were obtained at baseline and after 2 years of treatment. There were 56 paired biopsies evaluable for all indices. In raloxifene-treated patients, there were significant decreases in bone formation rate per tissue volume, consistent with a reduction in bone turnover. 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 tissue- and cellular-level effects of raloxifene were assessed by quantitative measurements (bone histomorphometry) on animal bones and human iliac crest bone biopsies taken after administration of a fluorochrome substance to label areas of mineralizing bone. The effects of raloxifene on bone histomorphometry were determined by pre- and post-treatment biopsies in a 6-month study of postmenopausal women. Bone in raloxifene-treated women was histologically normal, showing no evidence of mineralization defects, woven bone, or marrow fibrosis. The patterns of change were consistent with reduced bone turnover, although most changes were not statistically significant. In another bone histomorphometry study, postmenopausal women were treated for 6 months with raloxifene HCl at a higher dose (150 mg/day). Bone was also histologically normal, with no woven bone, marrow fibrosis, or mineralization defects.

In rats, raloxifene prevented increased bone resorption and bone loss after ovariectomy, and preserved bone strength in biomechanical studies. Ovariectomized cynomolgus monkeys were treated with raloxifene for 2 years, equivalent at the bone level to 6 years in humans. The biomechanical properties of bone from the raloxifene-treated monkeys were normal. Histologic examination of bone from rats and monkeys treated with raloxifene showed normal cancellous bone morphology, and no evidence of woven bone, marrow fibrosis, or mineralization defects.

The animal and human bone histomorphometric results are consistent with data from studies of radiocalcium kinetics and markers of bone metabolism, and demonstrate that raloxifene is a skeletal antiresorptive agent.

Effects on Lipid Metabolism

In animal studies, the effects of raloxifene on cholesterol metabolism were mediated through the estrogen receptor.

The effects of raloxifene on cardiovascular intermediate endpoints were evaluated in a 6-month study of 390 postmenopausal women. Raloxifene was compared with continuous combined estrogen/progestin (0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate, [HRT]) and placebo (Table 9. Raloxifene decreased serum total and LDL cholesterol without significant effects on serum total HDL cholesterol or triglycerides. Raloxifene significantly increased HDL-2 cholesterol subfraction. In addition, raloxifene significantly decreased serum fibrinogen and lipoprotein (a).

Table 9 Raloxifene and HRT Effects on Cardiovascular Intermediate Endpoints in a 6-Month Study -- Median Percentage Change from Baseline

	Treatment Group		
Endpoint	**Placebo (N=98) %**	**Raloxifene (N=95) %**	**HRT (N=96) %**
Total Cholesterol	0.9	-6.6	-4.4
LDL Cholesterol	1.0	-10.9	-12.7
HDL Cholesterol	0.9	0.7	10.6
HDL-2 Cholesterol	0.0	15.4	33.3
Fibrinogen	-2.1	-12.2	-2.8
Lipoprotein (a)	3.3	-4.1	-16.3
Triglycerides	-0.3	-4.1	20.0

Abbreviations: HRT = continuous combined estrogen/progestin (0.625 mg conjugated equine plus 2.5 mg medroxyprogesterone acetate).

Consistent with results from the 6-month study, in the osteoporosis treatment (36 months) and prevention (24 months) studies raloxifene significantly decreased serum total and LDL cholesterol, but did not increase HDL cholesterol or triglycerides. In the osteoporosis treatment study, significantly fewer raloxifene-treated patients required initiation of hypolipidemic therapy compared to placebo.

Effects on the Uterus

Postmenopausal estrogen deficiency leads to endometrial atrophy. Estrogen replacement therapy is associated with endometrial proliferation and hyperplasia, and increased risk of endometrial carcinoma. All forms of hormone replacement therapy are often accompanied by spotting and bleeding. In contrast, raloxifene has no endometrial stimulatory effect and does not induce spotting or bleeding.

In the osteoporosis treatment trial, endometrial thickness was evaluated annually in a subset of the study population (1781 patients) for 3 years. Endometrial thickness measurements in raloxifene-treated women were not different from baseline after 3 years of therapy. Placebo-treated women had a 0.27 mm decrease from baseline in endometrial thickness over 3 years. There was no difference between raloxifene- and placebo-treated women in the incidences of endometrial carcinoma, vaginal bleeding or vaginal discharge.

In placebo-controlled osteoporosis prevention trials, endometrial thickness was evaluated every 6 months (for 24 months) by transvaginal ultrasonography (TVU), a non-invasive method of visualizing the uterus. A total of 2,978 TVU measurements were collected from 831 women in all dose groups. Raloxifene-treated women consistently had endometrial thickness measurements indistinguishable from placebo. Furthermore, there were no differences between the raloxifene and placebo groups with respect to the incidence of reported vaginal bleeding.

In a 6-month study comparing raloxifene to conjugated equine estrogens (0.625 mg/day [ERT]), endpoint endometrial biopsies demonstrated stimulatory effects of ERT which were not observed for raloxifene (Table 10). All samples from raloxifene-treated women showed nonproliferative endometrium.

Table 10 Raloxifene and ERT Effects on Endometrial Histology After 6-Months of Therapy

	Treatment Group	
Endpoint Biopsy Result	**Raloxifene (N=10)**	**ERT (N=8)**
Nonproliferative Endometrium[a]	10	2
Proliferative Tissue	0	4
Simple Hyperplasia	0	2

Abbreviations: ERT = conjugated equine estrogens (0.625 mg/day).

[a] The term nonproliferative endometrium includes endometrial atrophy, surface endometrium, and inadequate sample.

A 12-month study of uterine effects compared a higher dose of raloxifene HC1 (150 mg/day) with HRT. At baseline, 43 raloxifene-treated women and 37 HRT-treated women had a nonproliferative endometrium. At study completion, endometrium in all of the raloxifene-treated women remained nonproliferative whereas 13 HRT-treated women had developed proliferative changes. Also, HRT significantly increased uterine volume; raloxifene did not increase uterine volume. Thus, no stimulatory effect of raloxifene on the endometrium was detected at more than twice the recommended dose.

The postmenopausal endometrium is atrophic due to the lack of endogenous estrogen. Consequently, the estrogen antagonist effects of raloxifene on this tissue could not be demonstrated in the clinical trials. However, raloxifene is a potent estrogen antagonist in the rat uterus, where it completely blocks the stimulatory effects of estrogen. In the absence of estrogen stimulation, raloxifene did not have any stimulatory effects on the endometrium in any animal models tested.

Effects on the Breast

Estrogen replacement therapy and hormone replacement therapy stimulate glandular and stromal components of breast tissue, resulting in symptoms of breast pain and tenderness in some postmenopausal women. In contrast, 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. Raloxifene was associated with significantly fewer breast symptoms than reported by women receiving estrogens with or without added progestin (see ADVERSE REACTIONS).

The estrogen antagonist aspects of raloxifene's SERM profile were examined in a variety of preclinical breast cancer models. Raloxifene inhibited the growth of MCF-7 human breast cancer cells *in vitro* and of MCF-7 xenograft tumours in mice. In animal models of carcinogen induced breast cancer (nitrosomethylurea [NMU] and dimethylbenzanthracene (DMBA]), raloxifene decreased tumour burden.

In clinical trials with raloxifene involving 17,151 patients, at least 10,850 women were exposed to raloxifene for up to 58 months. There was a statistically significant reduction in the frequency of newly diagnosed breast cancers in raloxifene-treated women compared with placebo (see Additional Safety Information). A portion of these patients were assigned to an additional 4 year study and the results were consistent by the end of 8 years that breast cancer incidence was significantly lower in the treated group in comparison to the placebo group. These observations are consistent with the preclinical pharmacologic profile of raloxifene (selective estrogen receptor modulator) and support the conclusion that raloxifene has no intrinsic estrogen agonist activity in mammary tissue. The long-term effectiveness of raloxifene in reducing the risk of breast cancer has not been fully established.

STORAGE AND STABILITY

Store at room temperature, 15° to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-RALOXIFENE 60 mg tablets: White, oval, biconvex tablets. Engraved "APO" on one side and "RAL 60" on the other side. Available in bottles of 100.

In addition to the active ingredient, raloxifene hydrochloride (60 mg), each tablet contains anhydrous lactose, crospovidone, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

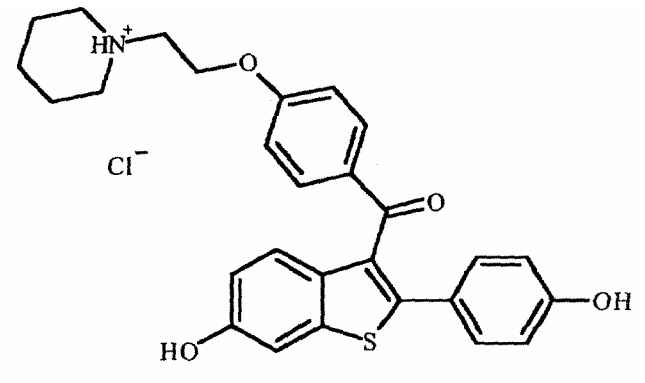
Drug Substance

Proper Name: raloxifene hydrochloride

Chemical Name: methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo[b] thien-3-yl]-[4-[2-(1 -piperidinyl)ethoxy]phenyl]-, hydrochloride

Molecular formula and molecular weight: $C_{28}H_{27}NO_4S \bullet HCl$, 510.05

Structural Formula:



Physicochemical properties: APO-RALOXIFENE is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The SERM profile of raloxifene includes estrogen agonist effects on bone and lipid metabolism but not in uterine or breast tissues. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

pH: 4.5 (25°C, saturated raloxifene hydrochloride solution in water)

pKa: 8.44, 9.12, and 10.0 (extrapolated aqueous pKa's)

Melting Point: 257.6-266.7°C

CLINICAL TRIALS

Comparative Bioavailability

A comparative bioavailability study was performed on healthy male volunteers under fasting conditions. The rate and extent of absorption of raloxifene was measured and compared following a single oral dose of APO-RALOXIFENE (raloxifene hydrochloride) or EVISTA® tablets. The results from measured data are summarized in Table 11:

Table 11 Comparative Bioavailability

Summary Table of the Comparative Bioavailability Data Raloxifene (Dose: 1 x 60 mg) From Measured Data - Under Fasting Conditions Based on Raloxifene				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
	Apo– Raloxifene	Evista®†		
AUC_{0-72} (pg•h/mL)	10120 11407 (54)	10261 11395 (47)	98.6	90.2 – 107.9
AUC_I (pg•h/mL)	12955 11947 (61)	13197 19532 (156)	101.0	79.9 – 127.6
C_{MAX} (pg/mL)	265 304 (53)	269 309 (65)	98.6	87.6 – 111.0
T_{MAX}^* (h)	13.1 (94)	11.5 (107)		
$T_{½}^*$ (h)	35.0 (67)	44.5 (161)		
* Expressed as arithmetic mean (CV%) only. ** Based on the least squares estimate. † Evista® (manufactured by Eli Lilly Canada Inc.) was purchased in Canada.				

DETAILED PHARMACOLOGY

Clinical Studies

In postmenopausal women with osteoporosis, APO-RALOXIFENE (raloxifene hydrochloride) reduces the risk of fractures. APO-RALOXIFENE also increases BMD of the spine, hip and total body. Similarly, in postmenopausal women without osteoporosis, APO-RALOXIFENE preserves bone mass and increases BMD relative to calcium alone at 24 months. The effect on hip bone mass is similar to that for the spine.

Treatment of Osteoporosis

In a large, well-controlled clinical trial, it was demonstrated that raloxifene decreases the risk of new vertebral fractures in osteoporotic postmenopausal women with and without prevalent vertebral fractures, and increases lumbar spine and femoral neck BMD significantly relative to placebo and baseline. Two support studies provided additional confirmation of the efficacy of raloxifene as a skeletal antiresorptive agent.

The primary osteoporosis treatment trial was a Phase 3, multicenter, double-blind, placebo-controlled, randomized, 36-month clinical study of raloxifene's effects in osteoporotic (low BMD and/or presence of baseline vertebral (T-4 through L-4 fractures) postmenopausal women. A total of 7705 postmenopausal women were randomly assigned to one of three treatment groups: placebo, raloxifene 60 mg/day, or raloxifene 120 mg/day. 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).

The incidence of new vertebral fractures was assessed by spinal radiographs after 2 and 3 years of treatment. Another primary objective was the assessment of lumbar spine and femoral neck BMD using dual x-ray absorptiometry. Spinal radiographs and BMD scans were reviewed centrally.

This 36-month analysis demonstrates that treatment of osteoporotic postmenopausal women with raloxifene HCl statistically significantly decreases the risk for roentgenographic and clinical vertebral fractures. Statistically significant reductions in the risk for new vertebral fractures were observed both in women with and without prevalent vertebral fractures, and these vertebral fracture risk reductions with raloxifene are clinically robust.

Treatment with raloxifene HCl resulted in no consistent statistically significant reductions in nonvertebral fracture. However, there were statistically significant decreases in the risk of fractures in composite endpoints including all clinically apparent fractures and fractures at the ankle. This study was not powered to see an effect at nonvertebral sites. Nonetheless, with increasing duration of treatment there were decreasing numbers of nonvertebral fractures with raloxifene compared to placebo.

Raloxifene treatment resulted in statistically significant increases in BMD (hip, total body, lumbar spine and ultradistal radius) or maintenance of BMD (distal 1/3 radius) and statistically significant decreases in all of the biochemical markers of bone metabolism, consistent with the antiresorptive mechanism of action of raloxifene. Importantly, the reductions in the biochemical markers of bone metabolism were not excessive; the suppression was similar to the mean levels for normal premenopausal women.

Statistically significant and clinically favorable decreases in total cholesterol, LDL-C, fibrinogen, and apolipoprotein B and increases in apolipoprotein A_1 were observed with 36 months of treatment with raloxifene HCl. No statistically significant changes in HDL-C or glycosylated hemoglobin occurred with raloxifene therapy. Median triglyceride concentration decreased in all groups, but the decrease was greater in the placebo group.

Treatment with raloxifene resulted in no clinically significant beneficial or adverse effects on cognitive and neuropsychomotor function.

Venous thromboembolism (VTE) was the only serious adverse event associated with raloxifene treatment, and the risk of developing VTE was increased approximately 3-fold with raloxifene use in postmenopausal women. However, the increased risk of developing VTE with raloxifene use is similar to the increased risk of developing VTE with postmenopausal use of HRT or tamoxifen.

The incidence of breast cancer was markedly decreased among women assigned to raloxifene treatment compared with placebo treatment, and the data strongly suggest that raloxifene had a protective effect with respect to invasive, estrogen-receptor positive breast carcinoma.

There was no increase in the incidence of uterine bleeding among postmenopausal women treated with raloxifene. Sonographic and histological data demonstrated a non-stimulatory effect on the endometrium. Furthermore, analysis of uterine cancer cases shows no association between raloxifene treatment and development of endometrial carcinoma. There was no increase in the reporting of ovarian carcinoma with raloxifene.

Two adverse events with an incidence of >2% are considered to be related to raloxifene use: vasodilatation and leg cramps. Vasodilafation is a common symptom of the climacteric and raloxifene appears to be an estrogen antagonist for this adverse event.

Vital signs, weight, and height were not affected in a clinically relevant manner by raloxifene use.

There were clinically significant reductions in alkaline phosphatase and inorganic phosphorus, consistent with a skeletal antiresorptive effect of raloxifene.

Prevention of Osteoporosis

The efficacy of raloxifene once daily in the prevention of osteoporosis was established over a 24-month treatment period in three well-controlled studies.

The studies randomized a total of 1764 women to therapy with active treatment or placebo A calcium supplement was provided to both placebo and treated subjects in these trials. Two of the studies (conducted in North America and Europe) were initiated using doses of 30 mg/day, 60 mg/day and 150 mg/day with the intent of demonstrating the efficacy of raloxifene HCl in preventing bone loss in early postmenopausal women with low or normal BMD. A third, international study had similar entry criteria based on BMD (lumbar spine BMD T-score of -2.5 to +2.0), but was performed in women who had previously undergone a hysterectomy, included younger women, had an estrogen comparator arm (conjugated equine estrogen [ERT] 0.625 mg/day), and did not include a raloxifene HCl 30-mg dose group.

The primary efficacy analyses in all studies included the comparison of baseline to endpoint change in lumbar spine and total hip BMD, as measured by dual-energy x-ray absorptiometry (DXA). The results from each of these studies clearly demonstrate that raloxifene therapy, compared with baseline and with calcium-supplemented placebo, resulted in statistically significant increases in BMD for almost all skeletal sites measured at each dose examined, and is an effective agent for the prevention of bone loss.

As expected with therapies which decrease bone resorption, a significant effect on BMD was observed within several months of initiation of therapy and persisted throughout the studies. The results consistently demonstrated a statistically significant therapy effect at the hip, where fractures result in substantial morbidity and mortality. Furthermore, measurements of total body bone mineral content (BMC) by DXA demonstrated that there was a complete and statistically significant conservation or increase in total body BMC in raloxifene-treated subjects, whereas there was statistically significant loss of total body BMC in the calcium-supplemented placebo groups.

In all three studies, biochemical markers of bone metabolism were utilized to determine the effect of therapy on bone turnover. Although some variability in the performance of the markers was observed between studies, overall there was clear evidence for suppression of bone resorption in the raloxifene-therapy groups as assessed by urinary Type I collagen fragment-to-creatinine ratios, and bone formation, as assessed by bone specific alkaline phosphatase and osteocalcin concentrations. In the international study, the decreases in levels of biochemical markers of bone metabolism were greater in the group randomized to therapy with ERT.

Three supporting studies provided additional evidence for the efficacy of raloxifene in preventing bone loss. The results of these studies strongly support the data from the osteoporosis prevention studies and demonstrate that raloxifene: (1) has an estrogen-like effect on bone remodeling kinetics, particularly in decreasing bone turnover and resorption; (2) maintains bone quality and has consistent effects on bone histomorphometry; (3) preserves bone mass at both the hip and the lumbar spine in an older postmenopausal women; (4) reduces biochemical markers of bone metabolism into the range seen in premenopausal women (as one would expect from an estrogen-like drug) (multiple studies); and (5) decreases total cholesterol, LDL-C, and fibrinogen without increasing serum triglycerides.

Serum lipid levels were measured as secondary endpoints in the three osteoporosis prevention studies and as primary endpoints in a 6-month study of 390 postmenopausal women. These studies demonstrated that therapy with raloxifene resulted in significant and dose-related reductions in serum total cholesterol and LDL-C concentrations, similar to that seen with HRT. There were no significant change in HDL-C concentrations nor in serum triglyceride concentrations during therapy with raloxifene. However, raloxifene significantly increased HDL-C2 subfraction and lowered fibrinogen and lipoprotein (a) levels compared with placebo.

Raloxifene appears to have no estrogen agonist activity in the uterus. In ongoing trials, endometrial thickness was extensively evaluated using transvaginal ultrasound, a sensitive technique for detecting changes in endometrial thickness. No differences in endometrial thickness were observed between raloxifene- and placebo-treated patients with therapy duration up to 2 years. Furthermore, in contrast to the proliferative endometrial effects observed with continuous combined estrogen/progestin therapy, raloxifene therapy resulted in a decreased uterine volume and no evidence of a proliferative effect. In addition, raloxifene-treated patients reported an extremely low rate of uterine bleeding, no different from placebo, in contrast to the high rate of uterine bleeding observed in continuous combined HRT-treated patients.

In a 6-month study comparing raloxifene to conjugated equine estrogens (0.625 mg/day [ERT]), endpoint endometrial biopsies demonstrated stimulatory effects of ERT which were not observed for raloxifene. All samples from raloxifene-treated women showed nonproliferative endometrium.

Raloxifene also appears to have no estrogen agonist activity in the breast. The incidence of breast-related adverse events in raloxifene-treated women was not greater than for placebo-treated women in contrast to the observed increase in these adverse events in HRT/ERT-treated women. In ongoing studies of over 12,000 women, raloxifene was associated with a statistically significant reduction in the frequency of newly diagnosed breast cancer compared with placebo. These clinical observations support the nonclinical pharmacological profile demonstrating antiproliferative activity in breast tissue.

Additional clinical Trial Information

Breast: All cases of breast cancer in women enrolled in clinical trials were reviewed without knowledge of treatment status (blinded) by an independent Adjudication Review board. In a large 4-year randomized, placebo-controlled osteoporosis treatment trial, raloxifene compared to placebo reduced the incidence of invasive breast cancer by 72% (RR 0.28; 95% CI 0.17 - 0.46). The incidence rates were 5.3 per 1000 women-years for placebo, and 1.9 per 1000 women years for raloxifene. A portion of these patients participated in a 4-year placebo-controlled follow-up study. During the 4-year follow-up, raloxifene compared to placebo reduced the incidence of invasive breast cancer by 59% (HR 0.41; 95% CI 0.24-0.71). For the combined 8-year period, raloxifene reduced invasive breast cancer by 66% compared to placebo (HR 0.34; 95% CI 0.22-0.50). The long-term effectiveness of raloxifene in reducing the risk of breast cancer has not been fully established.

Cardiovascular: In placebo-controlled clinical trials ranging from 6 months to 5 years in duration, raloxifene has been shown to have no significant effect on C-reactive protein, and to significantly lower LDL-cholesterol without changing HDL-cholesterol or triglyceride concentrations. In a large 4-year randomized, placebo-controlled osteoporosis treatment trial, there were no significant differences between raloxifene and placebo in the overall cohort with respect to combined coronary and cerebrovascular events. In a subset of 1035 women with increased baseline cardiovascular risk, those assigned to raloxifene had a significantly lower risk of combined CV events compared to placebo (RR 0.60; 95% CI 0.38-0.95 for both raloxifene groups).

Pharmacokinetics

The disposition of raloxifene has been evaluated in more than 3000 postmenopausal women in selected raloxifene osteoporosis treatment and prevention clinical trials using a population approach. Pharmacokinetic data were also obtained in conventional clinical pharmacology studies in 292 postmenopausal women. Raloxifene exhibits high within-subject variability (approximately 30%) of most pharmacokinetic parameters.

APO-RALOXIFENE may be administered without regard to food intake, age, body weight, cigarette smoking, ethnic origin, alcohol use and decreased renal function associated with aging. Other than cholestyramine, raloxifene may be administered without regard to highly glucuronidated drugs, highly protein bound drugs, and numerous other concomitant medications.

Absorption: Raloxifene is absorbed rapidly after oral administration. The extent of absorption is estimated to be 60%. Presystemic glucuronidation is extensive resulting in a low absolute bioavailability of raloxifene of 2.0%. The plasma profile of orally administered raloxifene hydrochloride is consistent with enterohepatic circulation of raloxifene which involves the biliary excretion of raloxifene glucuronides, their hydrolysis by the gastrointestinal flora and subsequent re-entry of unconjugated raloxifene into the portal circulation.

Distribution: Raloxifene is extensively distributed throughout the body, and the apparent volume of distribution at steady-state is 7.5 L/kg following IV administration. Raloxifene and monoglucuronide metabolites are highly bound to plasma proteins in vitro (>95%).

Metabolism: Raloxifene undergoes conjugation forming either raloxifene-6-glucuronide or raloxifene-4'-glucuronide, either of which can undergo further conjugation to form raloxifene-6,4'-diglucuronide. The raloxifene-4'-glucuronide is the most abundant metabolite. No other metabolites of raloxifene have been observed in plasma, urine, or feces. Raloxifene comprises approximately 1 % of the combined concentrations of raloxifene and its conjugated metabolites. Raloxifene levels are maintained by enterohepatic recycling, giving a plasma half-life of 27.7 hours.

Excretion: Following intravenous administration, raloxifene is cleared at a rate approximating hepatic blood flow. Less than 6% of a total administered dose is eliminated in the urine predominantly as the glucuronide conjugates of raloxifene. The majority of the dose of raloxifene and raloxifene metabolites is excreted within 5 days, primarily in the feces, suggesting the biliary excretion of glucuronide conjugates.

Animal Pharmacology

Effects on Bone

The effects of raloxitene on bone mass, architecture, and quality have been evaluated in young adult or aged rats that were ovariectomized and then orally dosed for up to 12 months. Bone densitometry and histomorphometry showed that raloxifene has efficacy comparable to 17α-ethynyl estradiol or 17β-estradiol in preventing the loss of trabecular bone resulting from ovariectomy. Biomechanical analyses of bone quality showed that raloxifene is as efficacious as 17α-ethynyl estradiol in maintaining the mechanical integrity and strength of the lumbar vertebrae, femoral neck, and femoral diaphysis. Bone densitometry of lumbar vertebrae, distal femora, or proximal tibiae suggested that raloxifene HCl has maximal efficacy at a dose of 1 mg/kg, and half-maximal efficacy (ED50) at 0.3 mg/kg. *In vivo* potency differences between raloxifene and estrogen were observed, with 17α-ethynyl estradiol more potent than raloxifene. Serum and urinary biochemical markers of bone metabolism also showed that the effects of raloxifene parallel those of estrogen in OVX rats.

A similar pattern of activity was observed in OVX cynomolgus monkeys. Over a 2-year treatment period in OVX cynomolgus monkeys, raloxifene blunted the ovariectomy-induced elevation of circulating markers of bone metabolism and produced higher vertebral bone mineral density (BMD) when compared with OVX controls. While ovariectomy was not associated with consistently significant deficiencies in biomechanical strength of bone in this study, a significant correlation was observed between vertebral strength and vertebral BMD in control, estrogen-, and raloxifene-treated OVX monkeys. A significant correlation was also observed in OVX rats. Furthermore, after the 2-year treatment period, biomechanical analysis of material properties of milled bone samples from monkeys revealed no adverse effects of raloxifene treatment on bone quality.

Histomorphometric evaluations in the OVX rat model showed that, similar to 17α-ethynyl estradiol, raloxifene blocks ovariectomy-stimulated bone resorption by inhibiting increases in osteoclast number, eroded perimeter, trabecular separation, and bone turnover. Raloxifene appears to have less suppressive effect on bone formation than estrogen under certain experimental conditions, although suppression of bone formation with raloxifene can be demonstrated in OVX rats and monkeys. Polarized light microscopy indicated that bone was of normal quality in the raloxifene-treated OVX monkeys following the 2-year treatment period, with no evidence of woven bone formation.

Collectively, these studies demonstrate that the raloxifene profile of effects on bone in rats and monkeys is very similar to that of estrogen.

Effects on the Cardiovascular System

The increased incidence of coronary heart disease in postmenopausal women is at least partially attributed to estrogen deficiency-induced changes in lipoprotein metabolism. Since the mechanisms by which estrogen lowers cholesterol in rats and humans are similar (i.e. induction of hepatic LDL receptors and enhanced clearance of LDL-C), the rat is a useful species in which to study the pharmacological effects of estrogen-like compounds on cholesterol homeostasis. Thus, the ability of estrogen and estrogen-like compounds to lower serum cholesterol in rats may be predictive of human effects.

In OVX rats, raloxifene produces a marked cholesterol-lowering effect similar to that of estrogen. After 5 weeks of treatment, raloxitene HCl significantly lowered serum cholesterol at oral doses as low as 0.1 mg/kg, with an ED50 of 0.2 mg/kg. This cholesterol-lowering activity was maintained during administration of raloxifene for up to 12 months. Dose-response curves for cholesterol lowering produced by 17α-ethynyl estradiol in the presence or absence of raloxifene indicated that cholesterol lowering by these two agents is not additive when one of them is present at a maximally effective dose. The cholesterol-lowering effect of raloxifene in rats appears to involve ER-mediated induction of hepatic LDL-receptors, leading to enhanced clearance of serum lipoproteins containing apolipoprotein B or apolipoprotein E.

Additionally, a similar reduction in serum total cholesterol was observed in OVX monkeys during 24 months of treatment with raloxifene HCl using dosages which produced plasma concentrations of raloxifene similar to those in postmenopausal women receiving 60 mg/day of the drug.

In cholesterol-fed OVX rabbits, treatment with raloxifene led to a significant reduction in the accumulation of aortic cholesterol. The magnitude of this reduction was less than that observed in similar rabbits treated with 17β-estradiol. However, the plasma concentrations of raloxifene achieved in this study were low, relative to plasma concentrations observed in clinical trials. Similar to the situation with estrogen, the effect of raloxifene on aortic cholesterol accumulation could not be fully explained by alterations in serum lipids alone. However, no reduction of a high-cholesterol-diet-induced thickening of coronary intima in monkeys was observed after treatment with raloxifene.

In addition to its cholesterol-lowering activity, raloxifene also produces other cardiovascular effects *in vitro* or in animal models which suggest cardiovascular protection. These include inhibition of endothelial cell activation, inhibition of smooth-muscle cell migration, inhibition of LDL oxidation, and inhibition of intimal thickening in response to balloon injury in rats. In ovariectomized cholesterol fed rabbits with pre-induced atherosclerosis, raloxifene and estradiol treatment for a 39 week period significantly reduced the progression of atherosclerosis ($p<0.01$) compared to placebo.

Effects on the Uterus

In estrogen deficient animals (rats, rabbits, monkeys) raloxifene fails to produce estrogen-like stimulation of the uterus. While a small, non-doserelated elevation of uterine weight has been observed in ovariectomized rats (an effect attributed to water retention in the stromal compartment), no stimulation of the endometrium or other estrogen-sensitive uterine markers (i.e. eosinophilia) was observed.

Raloxifene fails to mimic estrogen's stimulatory effect on the uterus; it is a potent and complete antagonist of estrogen induced uterine weight gain, eosinophilia, endometrial c-fos expression and glycogen synthesis. Raloxifene is unique among selective estrogen receptor modulators in this regard. The ability of raloxifene to function as a complete estrogen antagonist in the uterus is due to the lack of intrinsic activity at activating estrogen receptor mediated pathways in the uterus.

Effects on Mammary Tumours

Raloxifene completely antagonizes the proliferation of ER-dependent mammary tumour cells, including the MCF-7 human cell line, with an inhibitory concentration for 50% inhibition (IC50) value of approximately 0.2 nM *in vitro.* The antiproliferative effect of raloxifene on estrogen-receptor-positive human breast cancer cell lines can be demonstrated in the presence of added estrogen, but raloxifene produces no proliferative effect when administered to these cells in the absence of estrogen (ie, lack of direct estrogen agonist activity). As might be expected, raloxifene has no antiproliferative activity against nonestrogen-dependent mammary carcinoma lines, such as the androgen-sensitive Shionogi mouse mammary carcinoma. *In vivo,* raloxifene effectively antagonizes the growth of established mammary tumours induced by carcinogens, (ie, dimethylbenzanthracene [DMBA]) or implanted as xenografts in athymic mice (ie, MCF-7). Raloxifene also prevents the development of mammary tumours induced by the chemical carcinogen nitrosomethylurea (NMU). In this prevention model, raloxifene (at 20 mg/kg orally) reduced tumour incidence by 57% and tumour burden by 82%.

Detailed Pharmacology

Thrombomodulin

An in vitro study in human umbilical vein endothelial cells has demonstrated the effect of raloxifene on upregulating thrombomodulin, which results in an enhancing of the anticoagulant properties of unstimulated and IL-1 -activated endothelial cells. Tlirombomodulin is involved in the feedback mechanism of the coagulation cascade and studies have indicated that impaired expression of thrombomodulin may contribute to an increased risk for cardiovascular disease. The extent to which the observed effects of raloxifene on thrombomodulin activity occur *in vivo* is unknown.

TOXICOLOGY

Acute Toxicity

No mortality occurred in mice or rats administered single 5000-mg/kg oral doses of raloxifene HCl. An intraperitoneal dose of 2000 mg/kg given to rats produced 20% mortality. Clinical signs were limited to leg weakness, soft stools, and compound-colored feces in rats given raloxifene orally and to leg weakness, hypoactivity, and poor grooming in rats given the compound parenterally. No effects were seen in dogs or monkeys given a single oral dose of 300 mg/kg. Rhesus monkeys tolerated a single 300-mg/kg dose of raloxifene without developing any physical signs of toxicity.

Repeated-Dose Toxicity

B6C3F1 mice administered raloxifene HCl in the diet for 3 months at average daily doses up to approximately 120 mg/kg had decreases in body weight gain with no associated toxicologically important effects. The most notable treatment-related finding was the estrogen antagonist effect of decreased uterine weight. The 6-month and 1-year dietary studies in Fischer 344 rats at doses up to approximately 25 mg/kg produced similar findings.

In males, there were treatment-related decreases in food consumption and body weight gain. In female rats, decreased uterine weights and moderate elevations in serum alkaline phosphatase occurred at all doses. Moderate increases in adrenal weights were also seen in rats that received raloxifene, but these increases were not associated with any substantive histologic changes. Mineralization of the corticomedullary tubules of the kidneys occurred in both male and female rats of all dose groups. in a 6-month study in dogs at doses up to 30 mg/kg, the only treatment-related findings were decreased prostate weights in 2 of the 4 high-dose dogs, and aspermatogenesis and slight prostatic atrophy in 1 of those 2 dogs. The effects on the prostate are consistent with the pharmacologic activity of raloxifene. No effects were observed in female dogs. There were no proliferative changes and no ocular effects in the chronic studies in rats and dogs.

In subchronic studies conducted with CD-1 mice, Fischer 344 rats, and cynomolgus monkeys using raloxifene doses up to approximately 1700, 700, and 1000 mg/kg, respectively, results were similar to those of the subchronic and chronic studies described previously. The primary findings in rodents included reduced food consumption and reduced body weight; decreased uterine and pituitary weights; and uterine hypoplasia, vaginal mucoid metaplasia, and ovarian changes. However, in female mice, body weight was increased at raloxifene doses ≥184 mg/kg. The most important effects seen in monkeys treated for 1 month were decreased food consumption, various stool abnormalities in high-dose animals, and reduced thymus weights in males. At all doses, reduced uterine weights and ovarian cysts were observed. With the exception of the abnormal stools in monkeys given 1000 mg/kg, all of the changes produced by raloxifene treatment were attributable to its estrogen agonist/antagonist activity.

A 1-year toxicity study was conducted in cynomolgus monkeys to evaluate the effects of raloxifene HCl on intact females, OVX females, and juvenile males at daily raloxifene doses of 0, 15, 30, or 100 mg/kg. Increases (2- to 6-fold above control values) in serum alanine transaminase (ALT) were observed in all groups of raloxifene-treated OVX females, but only in the mid-and high-dose groups of intact females. Serum ALT values in males were unaffected. Other serum enzymes associated with impaired liver function were not similarly increased, and there were no significant morphologic hepatocellular changes in any treated animals. Because estrogen has been shown to induce elevations in serum transaminases in the absence of hepatocellular damage, the increased serum ALT values seen in this study were likely related to the estrogenic activity of raloxifene in the liver and were not an indicator of hepatocellular damage. Reduced uterine weight and generalized atrophy of the uterus occurred in intact females treated with raloxifene. In raloxifene-treated OVX females, the uteri were indistinguishable (in weight and morphology) from those of the OVX control group. Ovarian weights were significantly increased in the mid- and high-dose groups compared to the control. Ovaries in raloxifene-treated animals had developing follicles and/or corpora lutea, but no follicular cysts were seen in any treated animal. Pituitary weights were reduced in males at all dose levels and thymus weights were decreased in high-dose males, but neither of these changes was associated with any abnormal tissue morphology. There were no proliferative lesions in any tissues or organs and no ocular effects. All of the notable effects in this study were attributable to raloxifene's pharmacologic activity as a SERM, and were not considered to represent toxicologically important findings.

Carcinogenesis, Teratogenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats, an increased incidence in ovarian tumours of granulosaltheca cell origin was observed in females given 279 mg/kg. Systemic exposure (AUC) of raloxifene in this group was approximately 400 times that in postmenopausal women administered a 60 mg dose. In a 21-month carcinogenicity study in mice, there was an increased incidence of testicular interstitial cell tumours and prostatic adenomas and adenocarcinomas in males given 41 or 210 mg/kg, and prostatic leiomyoblastoma in males given 210 mg/kg. In female mice, an increased incidence of ovarian tumours in animals given 9 to 242 mg/kg (0.3 to 32 times the AUC in humans) included benign and malignant tumours of granulosaltheca 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. In contrast to the highly responsive ovaries in this rodent model, the human ovary after menopause is relatively unresponsive to reproductive hormonal stimulation.

In teratology studies, a no-observed-effect level of 0.1 mg/kg raloxifene HCl was established for fetal effects in CD rats, but fetal abnormalities were observed at the lowest doses tested in two strains of rabbits. The developmental deviation in rats was wavy ribs. In Dutch Belted rabbits at a dose of 10 mg/kg and in New Zealand white rabbits at doses ≥0.1 mg/kg, developmental toxicity was manifested as a low incidence of hydrocephaly (3 out of 56), and as a ventricular septal defect of the heart (3 out of 338), respectively.

When male and female rats were given daily doses >5 mg/kg prior to and during mating, no pregnancies occurred. In male rats, daily doses up to 100 mg/kg for at least 2 weeks did not affect sperm production or quality, or reproductive performance. At doses of 0.1 to 10 mg/kg/day in female rats, raloxifene disrupted estrous cycles during treatment, but did not delay fertile matings after treatment termination and marginally decreased litter size, increased gestation length, and altered the timing of events in neonatal development. When given during the preimplantation period, raloxifene delayed and disrupted embryo implantation resulting in prolonged gestation and reduced litter size, but development of offspring to weaning was not affected. The reproductive and developmental effects observed in animals are consistent with the estrogen receptor activity of raloxifene.

Mutagenesis

Raloxifene HCl was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis with and without metabolic activation, the unscheduled DNA synthesis assay in rat hepatocytes, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, the *in vivo* sister chromatid exchange assay in Chinese hamsters, and the *in vivo* micronucleus test in mice. Raloxifene HCl did not cause formation of DNA adducts in the liver of rats given an intraperitoneal dose of 20 mg/kg.

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PART III: CONSUMER INFORMATION

[PR]APO-RALOXIFENE
Raloxifene Hydrochloride Tablets

This leaflet is part III of a three-part "Product Monograph" published when [PR]APO-RALOXIFENE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about [PR]APO-RALOXIFENE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
APO-RALOXIFENE is used to treat or prevent osteoporosis **in post-menopausal women**.

This information should answer some of the questions that you may have and help you to understand how to take APO-RALOXIFENE. If you still have any questions or concerns about taking this medication, talk to your doctor or pharmacist.

Keep this information with your medicine in case you need to read it again.

What it does:
APO-RALOXIFENE is the brand name of a substance called raloxifene made by Apotex Inc. Your doctor may also refer to APO-RALOXIFENE as a Selective Estrogen Receptor Modulator or SERM. APO-RALOXIFENE is not a hormone, but it acts like estrogen in some parts of your body including the bones, but not like estrogen in other parts of the body. In the bones it promotes the building of new bones, either to prevent or treat osteoporosis.

What is Osteoporosis?
Osteoporosis is a thinning and weakening of the bones making the bones more likely to break. It is common in women after the menopause or after the removal of the ovaries because of the decrease in estrogens. A variety of factors may promote osteoprosis. These include:

- Caucasian or Asian descent
- Slender build
- Early menopause
- Smoking
- Drinking alcohol
- A diet low in calcium
- Lack of exercise
- A family history of osteoporosis

Initially osteoporosis usually does not cause any symptoms, but if left untreated may result in fractures. While most fractures are painful, fractures of the spine may not be noticed until they result in loss of height or a stooped posture. The fractures may occur as the result of normal every day activity or from minor injuries, which would ordinarily not result in broken bone.

How can osteoporosis be prevented or treated?
Eat a balanced diet. Vitamin D and calcium are necessary for building strong bones. The requirement for vitamin D increases as you grow older. In the winter, when there is less sunlight, your skin produces less vitamin D. Discuss with your doctor the need to take vitamin D and calcium take vitamin D and calcium supplements.

1. Do not smoke.

2. Exercise. Bones need exercise to stay strong and healthy. Consult your doctor about an exercise program suitable to you.

3. While diet, exercise and vitamins are essential to good health, they may not be enough to offset the effects of estrogen decline in some women's bodies after menopause. Consequently, some people may require medications such as APO-RALOXIFENE to prevent or treat osteoporosis.

When it should not be used:
Do not use APO-RALOXIFENE if:

- You are allergic to raloxifene or any of the ingredients listed at the end of this information.
- You are pregnant or planning to become pregnant as Apo-Raloxifene could hart the unborn child.
- You are breastfeeding. It is not know if Apo-Raloxifene passes to breast milk and what effect it may have on the baby.
- You have or have had blood clots in the veins that require a doctor's treatment. Taking APO-RALOXIFENE may increase the risk of blood clots.

What the medicinal ingredient is:
Each tablet of APO-RALOXIFENE contains raloxifene as the active ingredient.

What the important nonmedicinal ingredients are:
Anhydrous lactose, crospovidone, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

What dosage forms it comes in:
60 mg tablets

WARNINGS AND PRECAUTIONS

Before starting [PR]APO-RALOXIFENE and to get the best possible treatment, be sure to tell your doctor if you:

- are pregnant, breast feeding, still have menstrual bleeds, or have had a menstrual bleed in the last year, as APO-RALOXIFENE is only for postmenopausal women.
- have had an allergic reaction to any medicine you have taken
- are intolerant to lactose because APO-RALOXIFENE contains lactose
- have or ever had liver problems
- have or ever had blood clots that have required a doctor's treatment, If you take warfarin (blood thinner) or other coumarin derivatives, APO-RALOXIFENE may not be suitable for you. It is contraindicated in women with an active or past history of blood clots in the veins, If you are taking the blood thinners for other reasons your doctor may need to check your prothrombin (blood clotting) time and adjust your medicine when you first begin taking APO-RALOXIFENE.
- are currently on any other medications, prescription or non prescription
- being immobile for a long time may increase the risk of blood clots in the vein. If while taking APO-RALOXIFENE you plan to be immobile, such as staying in bed after surgery, or taking a long plane trip, you should stop taking APO-RALOXIFENE at least 3 days before, as this may increase your risk of blood clots. When you are back on your feet, you may start taking APO-RALOXIFENE again.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor all the medicines that you are taking before starting to take APO-RALOXIFENE.

The effect of APO-RALOXIFENE is significantly reduced if taken with cholestyramine (products which contain cholestyramine include Questran®, Questran Light®, Alti-Cholestyramine Light, Novo-Cholamine, Novo-Cholamine Light, PMSCholestryramine). Therefore, you should not take cholestyramine while taking APO-RALOXIFENE.

It is not recommended that you combine APO-RALOXIFENE with hormone replacement therapy (ERT or HRT) since no studies have been done to look at the effectiveness or safety of this combination.

During clinical trials, APO-RALOXIFENE was taken with commonly prescribed medications such as acetaminophen, digoxin, nonsteroidal anti-inflammatory drugs (NSAIDS), and oral antibiotics with no observed problems. However, because each patient is different, you should always check with your doctor before taking any other medication.

PROPER USE OF THIS MEDICATION

Usual dose:
Take one APO-RALOXIFENE tablet, once-a-day, any time, with or without food. APO-RALOXIFENE comes in a 28-day blister pack that you start as soon as you fill your prescription. Each day of the week is printed above each tablet to make it easy to check if you've taken your pill that day.

You might find it helpful to take your tablet at the same time every day so that it's simply part of your routine. The efficacy of APO-RALOXIFENE is dependent upon your taking it regularly. Therefore, you should keep taking APO-RALOXIFENE until your doctor advises you otherwise.

If you miss a day of APO-RALOXIFENE take one pill as soon as you remember and resume one tablet once daily.

Overdose:
If you take too much, immediately contact your doctor or go to your nearest hospital emergency department. Show your doctor the bottle of medicine. Do this even if there are no signs of discomfort or poisoning.

Missed Dose:
Take your prescribed dose at the same time each day. If you miss a dose of APO-RALOXIFENE by a few hours, take the dose when you remember. If most of the day has passed, wait until your next scheduled dose and try not to miss any more. **Do not take 2 doses at once.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

During clinical trials, some women did have mild side effects such as hot flashes or leg cramps. However, most women did not find these side effects serious enough to stop taking APO-RALOXIFENE. Another common side effect is flu-like symptoms.

Similar to estrogen replacements, APO-RALOXIFENE may increase the risk of blood clots. Although this is a rare side effect, if you experience any unusual symptoms such as redness, swelling, heat or pain in your calves and legs, or sudden chest pain, shortness of breath, or a change in vision, talk to your doctor immediately.

APO-RALOXIFENE is not associated with adverse effects on the uterus, breast, or cognitive function. Therefore, any unexplained uterine bleeding, breast enlargement, breast pain, change in mood or deterioration of cognitive function should be reported to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Blood clots in the veins		*	*

This is not a complete list of side effects. For any unexpected effects while taking [PR]APO-RALOXIFENE, contact your doctor or pharmacist.

HOW TO STORE IT

All medicines should be stored out of the reach of children. APO-RALOXIFENE should be stored in its original package at room temperature in a dry place.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Canada
Address Locator: 0201C2
Ottawa, ON K1A 1B9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional. This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service, at 1-800-667-4708. This leaflet can also be found at http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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