# PRODUCT MONOGRAPH

## [Pr] TEVA-RALOXIFENE

(raloxifene hydrochloride)

60 mg Tablets

Selective Estrogen Receptor Modulator

**Teva Standard**

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**Control No. 148378**

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**Tablets**

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablet / 60 mg | Lactose<br>*For a complete listing see Dosage Forms, Composition and Packaging section* |

### INDICATIONS AND CLINICAL USE

TEVA-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.

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. 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 TEVA-RALOXIFENE for prevention of postmenopausal osteoporosis.

**Geriatrics:** Safety and efficacy in older and younger postmenopausal women in the osteoporosis treatment trial appear to be comparable (see WARNINGS AND PRECAUTIONS).

**Pediatrics**: The safety and efficacy of TEVA-RALOXIFENE have not been studied in pediatric populations. TEVA-RALOXIFENE should not be used in pediatric patients (see WARNINGS AND PRECAUTIONS).

## CONTRAINDICATIONS

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

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

TEVA-RALOXIFENE is contraindicated in patients known to be hypersensitive to raloxifene HCl or other constituents of the product. For a complete listing, see DOSAGE FORMS, COMPOSITION and PACKAGING section.

## WARNINGS AND PRECAUTIONS

### Venous Thromboembolic Events (VTE)

The risk-benefit balance should be considered in women at risk of thromboembolic disease for any reason. TEVA-RALOXIFENE should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g. post-surgical recovery, prolonged bed rest) and TEVA-RALOXIFENE therapy should be resumed only after the patient is fully ambulatory. In clinical trials, raloxifene HCl-treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism). VTE events reported in the osteoporosis treatment and prevention trials were infrequent (1.44, 3.32 and 3.63 events per 1,000 person-years for placebo, raloxifene HCl 60 mg/day and raloxifene HCl 120 mg/day, respectively). The incidence rate of VTE reported from the Raloxifene HCl Use for The Heart (RUTH) study was 2.70 and 3.88 events per 1,000 person-years for placebo and raloxifene HCl 60mg/day, respectively. Other venous thromboembolic events could also occur. A less serious event, superficial thrombophlebitis, also has been reported more frequently with raloxifene HCl. 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.

### Stroke

The risk-benefit balance of raloxifene HCl in postmenopausal women with a history of stroke or other significant stroke risk factors, such as transient ischemic attack or atrial fibrillation, should be considered when prescribing TEVA-RALOXIFENE. The RUTH trial investigated the effects of raloxifene HCl in postmenopausal women (average age = 67 years) with known heart disease or at high risk for a coronary event. The RUTH trial

demonstrated an increase in mortality due to stroke for raloxifene HCl compared to placebo. The incidence of stroke mortality was 1.5 per 1,000 women per year for placebo versus 2.2 per 1,000 women per year for raloxifene HCl (p=0.0499). The incidence of stroke, myocardial infarction, hospitalized acute coronary syndrome, cardiovascular mortality, or overall mortality (all causes combined) was comparable for raloxifene HCl and placebo.

**Premenopausal Use**

Safety of TEVA-RALOXIFENE in premenopausal women has not been established and its use is not indicated.

**Hepatic Dysfunction**

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

**General**

**Concurrent Estrogen Therapy**: Safety information regarding the concurrent use of Raloxifene HCl and systemic hormone therapy (estrogen with or without progestin) is limited and therefore concomitant use of raloxifene HCl with systemic estrogens is not recommended.

**Lipid Metabolism:** Raloxifene HCl 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 HCl. These effects should be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidemia. Concurrent use of raloxifene HCl and lipid lowering agents has not been studied.

**Endometrium:** Unexplained uterine bleeding should be investigated as clinically indicated.

**Breast**: Any unexplained breast abnormality occurring during TEVA-RALOXIFENE therapy should be investigated.

**Cognition and Affect:** Any change in cognition and affect during TEVA-RALOXIFENE therapy should be investigated as clinically indicated.

**Estrogen-Induced Hypertriglyceridemia**

Patients with a history of estrogen-induced hypertriglyceridemia can experience an increase in triglyceride levels during treatment with raloxifene HCl. Therefore, triglyceride levels should be followed in such patients and the risk-benefit balance of TEVA-RALOXIFENE treatment in such cases should be reassessed (see CLINICAL TRIALS).

## Information for Patients

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

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

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

**Use in Men**: There is no indication for use of TEVA-RALOXIFENE in men.

**Pediatric (< 18 years of age)**: TEVA-RALOXIFENE should not be used in pediatric patients.

**Geriatric**: 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**: TEVA-RALOXIFENE should not be used in women who are or may become pregnant (see CONTRAINDICATIONS).

**Nursing Women**: TEVA-RALOXIFENE should not be used by lactating women (see CONTRAINDICATIONS). It is not known whether raloxifene HCl is excreted in human milk.

### Premenopausal Use

Safety of TEVA-RALOXIFENE in premenopausal women has not been established and its use is not indicated.

**Monitoring and Laboratory Tests**

If TEVA-RALOXIFENE is given concomitantly with warfarin or other coumarin derivatives, the prothrombin time should be monitored when starting or stopping therapy with TEVA-RALOXIFENE (see DRUG INTERACTIONS section).

## ADVERSE REACTIONS

The safety of raloxifene HCl 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 HCl in the treatment of osteoporosis was assessed in a large, 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 HCl. In the osteoporosis treatment trial, 5129 women were exposed to raloxifene HCl (2557 received 60 mg/day and 2572 received 120 mg/day) for 36 months. The osteoporosis treatment trial was extended by 12 months to a 4th year during which patients were permitted the concomitant use of bisphosphonates, fluorides and calcitonins.

**Adverse Drug Reaction Overview**

The most commonly observed treatment-emergent adverse events associated with the use of raloxifene HCl in double-blind, placebo-controlled, osteoporosis treatment and prevention clinical trials were vasodilatation and leg cramps.

Vasodilatation events (hot flashes or flushes) were common in placebo-treated women, and the frequency was modestly increased in raloxifene HCl -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.

Venous thromboembolism (VTE) and pulmonary embolism are uncommon but serious adverse events associated with raloxifene HCl therapy. The greatest risk for deep vein thrombosis and pulmonary embolism occurs during the first 4 months of treatment.

An increase in mortality due to stroke for raloxifene HCl compared to placebo was demonstrated in the RUTH trial which investigated the effects of raloxifene HCl in postmenopausal women (average age = 67 years) with known heart disease or at high risk for a coronary event. (see WARNINGS AND PRECAUTIONS).

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

## Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction 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 clinical trials is useful for identifying drug-related adverse events and for approximating rates.

## Adverse Events in Placebo-Controlled Clinical Trials

Table 1 lists adverse events occurring in either the osteoporosis treatment (up to 3 years) or prevention placebo-controlled clinical trials with raloxifene HCl at a frequency ≥1.0% in raloxifene HCl -treated women and at a significantly greater incidence than in placebo-treated women.

**Table 1: Adverse Events Occurring in Placebo-Controlled Osteoporosis Clinical Trials (up to 36 months) at a Frequency ≥1.0% in Raloxifene HCl -Treated (60 mg once daily) Women and at a Significantly Greater Incidence Than in Placebo-Treated Women**

| | Osteoporosis Treatment | | Osteoporosis Prevention | |
|---|---|---|---|---|
| **Body System** | **Raloxifene HCl N=2557 %** | **Placebo N=2576 %** | **Raloxifene HCl N=581 %** | **Placebo N=584 %** |
| ***Body as a Whole*** | | | | |
| Flu Syndrome | 13.5* | 11.4 | 14.6 | 13.5 |
| Leg Cramps | 7.0* | 3.7 | 5.9* | 1.9 |
| ***Cardiovascular*** | | | | |
| Vasodilation | 9.7* | 6.4 | 24.6 | 18.3 |
| ***Metabolic and Nutritional*** | | | | |
| Diabetes Mellitus | 1.2* | 0.5 | A | A |

A Placebo incidence greater than or equal to raloxifene HCl incidence.

* Significantly ($p<0.05$) different from placebo.

**Glycemic Control:** Diabetes mellitus was reported more frequently as an adverse event among raloxifene HCl -treated patients (1.2%) compared with placebo-treated patients (0.5%) in the osteoporosis treatment trial. However, there were no differences between the raloxifene HCl and placebo groups in either fasting glucose or hemoglobin A1c (objective measures of glycemic control) in the osteoporosis treatment trial.

**Peripheral Edema in the Treatment and Prevention Trials**: A significant dose trend was observed for peripheral edema in the treatment and prevention studies. Cumulative frequency of the event at the 60 mg/day dose was 5.2% for raloxifene HCl-treated patients versus 4.4% for placebo-treated patients in the treatment study, and 3.1% for raloxifene HCl-treated patients versus 1.9% for placebo-treated patients in the prevention studies, which was not a statistically significant difference.

## 48-Month Osteoporosis Treatment Trial Adverse Events

The osteoporosis treatment trial was extended by 12 months to a 4th year during which patients were permitted the concomitant use of bisphosphonates, fluorides and calcitonins. The incidence trend of treatment-emergent adverse events occurring at a frequency ≥1.0% in raloxifene HCl-treated women, and at a significantly greater

incidence than in placebo-treated women after year 4 of the osteoporosis treatment trial, were generally similar to the 1 to 3 year results presented in Table 1.

At 48 months in the osteoporosis treatment trial, vasodilatation was reported in 10.6% of patients on raloxifene HCl versus 7.1% of placebo patients ($p<0.001$), and leg cramps were reported in 9.2% of patients on raloxifene HCl versus 6.0% of placebo patients ($p<0.001$).

At 48 months in the same osteoporosis treatment trial, flu syndrome (16.2% of raloxifene HCl treated patients versus 14.0% of placebo patients), uterine disorder (endometrial cavity fluid in 12.7% of raloxifene HCl treated patients versus 9.6% of placebo patients), diabetes mellitus (1.5% of raloxifene HCl treated patients versus 0.7% of placebo patients), and peripheral edema (7.1% of raloxifene HCl treated patients versus 6.1% of placebo patients) were also treatment-emergent adverse events which occurred more frequently with patients receiving raloxifene HCl compared to placebo ($p<0.05$).

**Adverse Reactions in a Placebo-Controlled Trial of Postmenopausal Women at Increased Risk for Major Coronary Events**

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

Adverse reactions reported at a frequency of ≥2.0%, which were considered to be possibly related to raloxifene HCl, and which occurred at a statistically significantly greater rate than placebo, were peripheral edema (14.1% raloxifene HCl versus 11.7% placebo), muscle spasms/leg cramps (12.1% raloxifene HCl versus 8.3% placebo), hot flashes (7.8% raloxifene HCl versus 4.7% placebo), venous thromboembolic events (2.0% raloxifene HCl versus 1.4% placebo), and cholelithiasis (3.3% raloxifene HCl versus 2.6% placebo). Although cholelithiasis was reported more frequently for raloxifene HCl than placebo, reports of cholecystectomy (2.3% raloxifene HCl versus 2.0% placebo) were not significantly different.

Bladder cancer was reported in 0.2% (10/5044) of patients on raloxifene HCl versus 0.1% (4/5057) of placebo patients in the RUTH trial. In an osteoporosis placebo-controlled treatment trial, bladder cancer was reported in 0.1% (3/5129) of patients on raloxifene HCl versus 0.2% (4/2576) of placebo patients.

**Comparison of Raloxifene HCl and Hormone Replacement Therapy Adverse Events**

Raloxifene HCl (N=317) was compared with continuous combined (N=96) hormone replacement therapy (HRT) or cyclic estrogen plus progestin HRT in 3 clinical trials for prevention of osteoporosis.

The incidence of breast pain (4.4% for raloxifene HCl-treated patients, 37.5% for continuous combined HRT-treated patients, and 29.7% for cyclic estrogen plus progestin HRT-treated patients), vaginal bleeding (6.2% for raloxifene HCl-treated patients, 64.2% for continuous combined HRT-treated patients and 88.5% for cyclic estrogen plus progestin HRT-treated patients), and abdominal pain (6.6% for raloxifene HCl-treated patients, 10.4% for continuous combined HRT-treated patients, and 18.7% for cyclic estrogen plus progestin HRT-treated patients) were significantly lower in raloxifene HCl-treated patients versus patients treated with either form of HRT ($p<0.05$).

Conversely, the incidence of vasodilatation (28.7% for raloxifene HCl-treated patients, 3.1% for continuous combined HRT-treated patients, and 5.9% for cyclic estrogen plus progestin HRT-treated patients) was significantly greater in raloxifene HCl-treated patients versus patients treated with either form of HRT ($p<0.05$).

**Laboratory Changes:** The following changes in analyte concentrations are commonly observed during raloxifene HCl therapy: increased serum HDL-2 cholesterol subfraction and apolipoprotein A1; and reduced serum total cholesterol, LDL cholesterol, fibrinogen, apolipoprotein B, and lipoprotein (a). Raloxifene HCl 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.

## DRUG INTERACTIONS

### Clinically Significant Drug-Drug Interactions

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

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

### Other Drug-Drug Interactions

***Ampicillin and Other Oral Antimicrobials:*** Peak concentrations of raloxifene HCl 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 HCl are not affected, raloxifene HCl 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 HCl concentrations.

***Corticosteroids:*** The chronic administration of raloxifene HCl in postmenopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose.

***Digoxin:*** Raloxifene HCl has no effect on the pharmacokinetics of digoxin. In the osteoporosis treatment trial, coadministered digoxin had no effect on plasma raloxifene HCl concentration.

***Gastrointestinal Medications:*** Concurrent administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene HCl. In the osteoporosis treatment trial, coadministered gastrointestinal medications (including bisacodyl, cisapride, docusate, H2-antagonists, laxatives, loperamide, omeprazole and psyllium) had no effect on plasma raloxifene HCl concentration.

***Highly Protein-Bound Drugs:*** Raloxifene HCl 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 HCl plasma concentrations was evaluated in the osteoporosis treatment trial. No clinically significant effects of these agents on raloxifene HCl plasma concentrations were identified. In vitro, raloxifene HCl did not affect the binding of phenytoin, tamoxifen or warfarin.

***Highly Glucuronidated Drugs:*** Raloxifene HCl undergoes extensive first-pass metabolism to glucuronide conjugates. The influence of co-administered highly glucuronidated drugs (including acetaminophen, ketoprofen, morphine and oxazepam) on raloxifene HCl plasma concentrations was evaluated in the osteoporosis treatment trial. No clinically significant effects of these agents on raloxifene HCl plasma concentrations were identified.

***Other Medications:*** The influence of concomitant medications on raloxifene HCl 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, H1-antagonists, H2- 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 HCl plasma concentrations were observed.

**Drug-Food Interactions**
TEVA-RALOXIFENE (raloxifene hydrochloride) can be administered without regard to meals.

**Drug-Laboratory Interactions**
Interactions with laboratory tests have not been established (see ADVERSE REACTIONS for additional laboratory safety information).

## DOSAGE AND ADMINISTRATION

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

**Missed Dose**
If a scheduled daily dose of TEVA-RALOXIFENE is missed, it should be taken as soon as remembered and one tablet once daily resumed. Do not take two doses at the same time.

## OVERDOSAGE

In an 8-week study of 63 postmenopausal women, a dose of raloxifene HCl 600 mg/day was safely tolerated. In clinical trials, no overdose of raloxifene HCl has been reported.

In postmarketing spontaneous reports, overdose has been reported very rarely (less than 1 out of 10,000 [<0.01%] patients treated). The highest overdose has been approximately 1.5 grams. No fatalities associated with overdose have been reported. In adults, symptoms reported in patients who took more than 120 mg as a single ingestion included leg cramps and dizziness. In some cases, no adverse events were reported as a result of the overdose.

In accidental overdose in children under 2 years of age, the maximum reported dose has been 180 mg. In children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhea, tremor, and flushing, as well as elevation in alkaline phosphatase.

There is no specific antidote for raloxifene HCl.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

**Pharmacodynamics**

## Mechanism of Action

Raloxifene HCl is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The SERM profile of raloxifene HCl includes estrogen agonist effects on bone and lipid metabolism, and estrogen antagonist effects in uterine and breast tissues. Raloxifene HCl'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.

## 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 HCl increases BMD to a lesser extent than estrogen, the effects of raloxifene HCl 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. Raloxifene HCl reduces biochemical markers of bone metabolism into the range seen in premenopausal women.

## Pharmacokinetics

The disposition of raloxifene HCl has been evaluated in more than 3000 postmenopausal women in selected raloxifene HCl 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 HCl exhibits high within-subject variability (approximately 30%) of most pharmacokinetic parameters. Table 2 summarizes the pharmacokinetic parameters of raloxifene HCl.

**Table 2: Summary of Raloxifene HCl 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<br>CV(%) | 0.50<br>52 | 27.7<br>10.7 to273[b] | 27.2<br>44 | 44.1<br>46 | 2348<br>52 |
| ***Multiple Dose*** | | | | | |

| | **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)** |
|---|---|---|---|---|---|
| Mean | 1.36 | 32.5 | 24.2 | 47.4 | 2853 |
| CV(%) | 37 | 15.8 to 86.6[b] | 36 | 41 | 56 |

*Abbreviations*: $C_{max}$ = 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 HCl is absorbed rapidly after oral administration. Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene HCl is 2.0%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene HCl and its glucuronide metabolites.

Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene HCl slightly, but does not lead to clinically meaningful changes in systemic exposure. Raloxifene HCl 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 HCl and the monoglucuronide conjugates are highly bound to plasma proteins. Raloxifene HCl binds to both albumin and αl-acid glycoprotein, but not to sex steroid binding globulin.

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

Following intravenous administration, raloxifene HCl is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/kg·hr. Raloxifene HCl 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 HCl 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 HCl is primarily excreted in feces, and negligible amounts are excreted unchanged in urine. Less than 6% of the raloxifene HCl dose is eliminated in urine as glucuronide conjugates.

**Special Populations and Conditions**

**Geriatrics:** The pharmacokinetics of raloxifene HCl are independent of age (42 to 84 years).

**Pediatrics:** The pharmacokinetics of raloxifene HCl 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 HCl plasma concentrations among these groups. The influence of race cannot be conclusively determined because of the small numbers of non-Caucasians.

**Renal Insufficienc**y: Since negligible amounts of raloxifene HCl are eliminated in urine, a study in patients with renal insufficiency was not conducted. In the osteoporosis treatment and prevention trials, raloxifene HCl 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). TEVA-RALOXIFENE should be used with caution in patients with moderate or severe renal impairment. Safety and efficacy have not been established in patients with moderate or severe renal impairment.

**Hepatic Insufficiency:** Raloxifene HCl was studied, as a single dose, in patients with Child-Pugh Class A cirrhosis with total serum bilirubin ranging from 0.6 to 2.0 mg/dL (10.3 to 34.2 μmol/L). Plasma raloxifene HCl 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 AND PRECAUTIONS).

## STORAGE AND STABILITY

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

## DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-RALOXIFENE is supplied in a tablet dosage form for oral administration. Each TEVA-RALOXIFENE tablet contains 60 mg of raloxifene hydrochloride. Inactive ingredients include colloidal anhydrous silica, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, polydextrose, povidone, pregelatinized starch and titanium dioxide.

TEVA-RALOXIFENE is available as:
**60 mg:** White to off-white, oval shaped, film-coated tablets, engraved with "60" on one side of the tablet and "N" on the other side of the tablet. Available in unit dose blisters of 30 tablets and bottles of 100.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

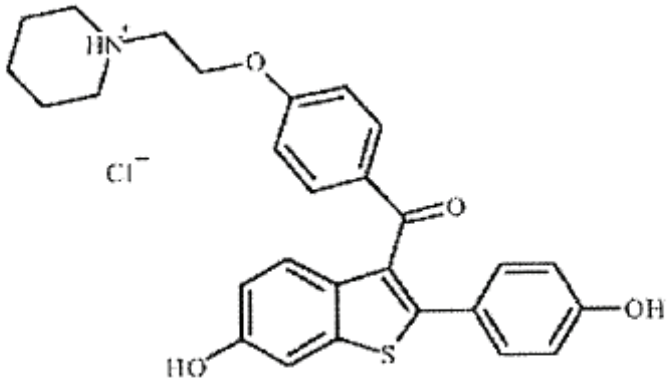
Common name: raloxifene hydrochloride

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

Molecular formula: $C_{28}H_{27}NO_4S \cdot HCl$

Molecular mass 510.05

Structural formula:




Physicochemical properties: Raloxifene hydrochloride is a pale yellow powder.

Solubility: Raloxifene hydrochloride is practically insoluble in water and methanol, freely soluble in N,N-dimethylformamide.

pH: The pH of a 2% (w/v) aqueous suspension is about 6.

Melting Point: 265°C (with decomposition).

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A single-dose, randomized, two-period, two-treatment, two-sequence crossover bioavailability study of Raloxifene hydrochloride 60 mg tablets (TEVA Pharmaceutical Industries Ltd.) and Evista® 60 mg tablets (Eli Lilly Canada Inc.) in 50 healthy, female subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

| Raloxifene HCl<br>(1 x 60 mg)<br>From measured data<br>**uncorrected for potency**<br>Geometric Mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | Test* | Reference† | % Ratio of Geometric Means | Confidence Interval, 90% |
| $AUC_{0-72}$ (ng*h/mL) | 12.2864<br>13.4949 (45) | 13.6030<br>14.6787 (39) | 90.32 | 83.27 – 97.98 |
| $AUC_I$ (ng*h/mL) | 19.3190<br>21.2643 (60) | 19.3614<br>22.3207 (56) | 99.78 | 89.01 – 111.86 |
| $C_{max}$ (ng/mL) | 0.3877<br>0.4843 (95) | 0.4515<br>0.5131 (53) | 85.88 | 75.55 – 97.63 |
| $T_{max}$§ (h) | 8.03 (89) | 7.19 (89) | | |
| $T_{½}$§ (h) | 44.38 (66) | 41.65 (80) | | |

* Raloxifene HCl 60 mg Tablets (Teva Pharmaceutical Industries Ltd.)
† Evista® 60 mg Tablets (Eli Lilly Canada Inc.) purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

## CLINICAL TRIALS

In postmenopausal women with osteoporosis, raloxifene HCl reduced the risk of fractures. Raloxifene HCl also increased BMD of the spine, hip and total body. Similarly, in postmenopausal women without osteoporosis, Raloxifene HCl preserved bone mass and increased BMD relative to calcium alone at 24 months. The effect on hip bone mass was similar to that for the spine.

**Treatment of Osteoporosis:** The effects of raloxifene HCl 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 HCl, 60 mg administered once daily, decreased the incidence of one or more vertebral fractures by as much as 55% (Table 3) and increased BMD compared to an active therapy of calcium plus vitamin D supplemented placebo. Raloxifene HCl 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 3: Effect of Raloxifene HCl on Risk of Vertebral Fractures**

| | Number of Patients | | Relative Risk |
|---|---|---|---|
| | **Raloxifene HCl** | **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 randomized 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.

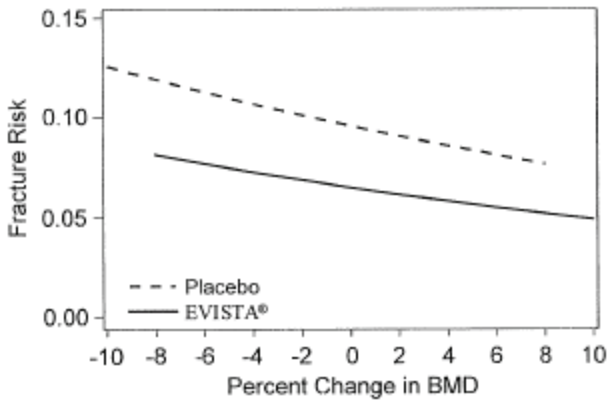



**Figure 1:** **Changes in BMD do not fully account for vertebral fracture risk reduction. This figure shows the correlation between vertebral fracture risk and percent change in femoral neck BMD at 3 years based on a logistic regression analysis of the clinical trial data. For any given change in BMD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

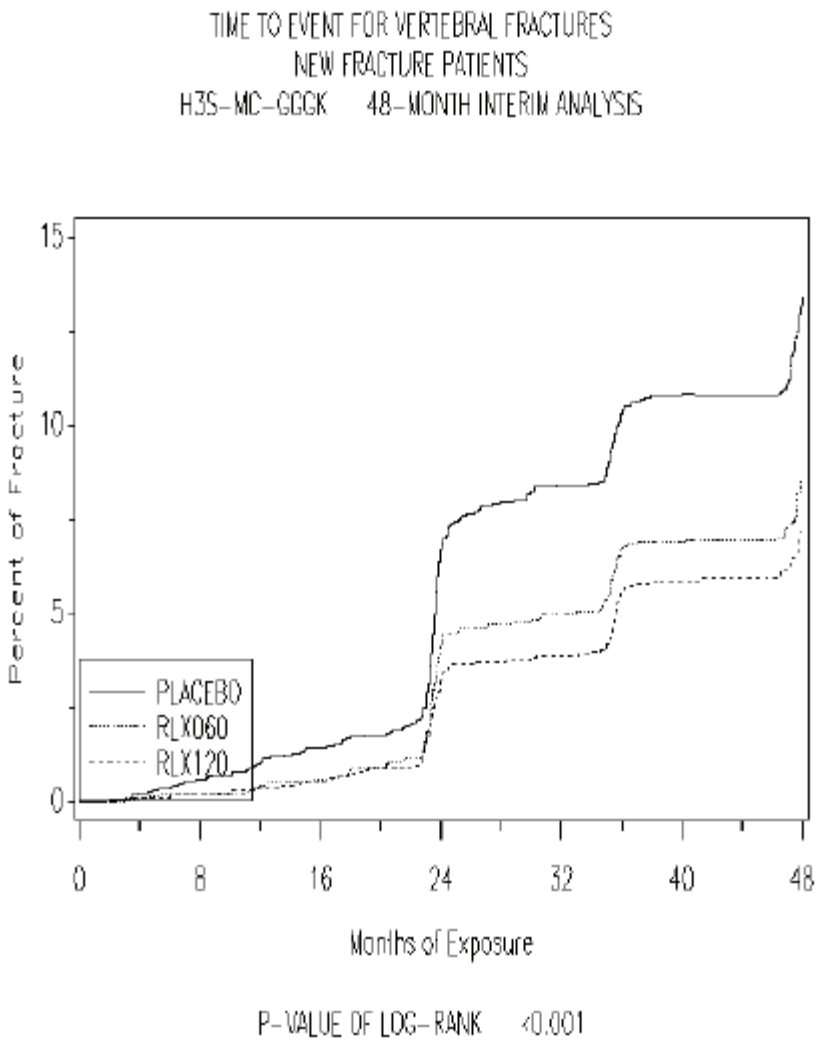



**Figure 2: Time to Event for Vertebral Fractures Over 48 Months**

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

At every time point, the mean percentage change in BMD from baseline for raloxifene HCl was significantly greater than for placebo at each skeletal site measured (Table 4).

**Table 4: Raloxifene HCl (60 mg once daily) related increases in BMD for the osteoporosis treatment study expressed as mean percentage increase versus calcium- and vitamin D-supplemented placebo[a]**

| Site | Time | | |
|---|---|---|---|
| | 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 HCl group (1.1%).

**Prevention of Osteoporosis:** The effects of raloxifene HCl 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).

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 5). In contrast, the calcium-supplemented placebo groups lost approximately 1% of BMD over 24 months.

**Table 5: Raloxifene HCl (60 mg once daily) Increases in BMD for the Three Osteoporosis Prevention Studies Expressed as Percentage Increase Versus Calcium-Supplemented Placebo at 24 Months**

| Site | Study | | |
|---|---|---|---|
| | NA % | 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: NA = North American, EU = European, INT = international.

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

Raloxifene HCl 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 HCl 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 HCl 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 HCl 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 (e.g., 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 HCl-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 HCl 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 HCl on bone histomorphometry were determined by pre- and post-treatment biopsies in a 6- month study of postmenopausal women. Bone in raloxifene HCl-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.

**Effects on Lipid Metabolism**

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 HCl therapy. In 2 of these 3 patients, serum triglyceride levels decreased while raloxifene HCl was continued. Patients with this medical history should have serum triglycerides monitored when taking raloxifene HCl.

**Effects on the Uterus**

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 HCl-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 HCl - 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 HCl -treated women consistently had endometrial thickness measurements indistinguishable from placebo. Furthermore, there were no differences between the raloxifene HCl and placebo groups with respect to the incidence of reported vaginal bleeding.

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

**Table 6: Raloxifene HCl and ERT Effects on Endometrial Histology After 6-Months of Therapy**

| | Treatment Group | |
|---|---|---|
| **Endpoint Biopsy Result** | **Raloxifene HCl (n=10)** | **ERT (n=8)** |
| Nonprofilerative Endometrium[a] | 10 | 2 |
| Proliferative Tissue | 0 | 4 |
| Simply 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 HCl (150 mg/day) with HRT. At baseline, 43 raloxifene HCl-treated women and 37 HRT-treated women had a nonproliferative endometrium. At study completion, endometrium in all of the raloxifene HCl-treated women remained nonproliferative whereas 13 HRT-treated women had developed proliferative changes. Also, HRT significantly increased uterine volume; raloxifene HCl did not increase uterine volume. Thus, no stimulatory effect of raloxifene HCl on the endometrium was detected at more than twice the recommended dose.

Raloxifene HCl does not increase the risk of ovarian carcinoma.

## Effects on the Breast

Across all placebo-controlled trials, raloxifene HCl was indistinguishable from placebo with regard to frequency and severity of breast symptoms. Raloxifene HCl was associated with significantly fewer breast symptoms than reported by women receiving estrogens with or without added progestin (see ADVERSE REACTIONS).

## Effects on the Central Nervous System

Raloxifene HCl has not been associated with deterioration of cognitive function or a change in affect. In the Multiple Outcomes of Raloxifene HCl Evaluation (MORE) trial, cognitive function was assessed as a secondary outcome in 7705 postmenopausal women with osteoporosis. Treatment with raloxifene HCl 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.

**Effects on the Cardiovascular System:**
In a large 4-year randomized, placebo-controlled osteoporosis treatment trial, there were no significant differences between raloxifene HCl and placebo in the overall cohort with respect to combined coronary and cerebrovascular events.

The risk-benefit balance of raloxifene HCl in postmenopausal women with a history of stroke or other significant stroke risk factors, such as transient ischemic attack or atrial fibrillation, should be considered when prescribing raloxifene HCl. The Raloxifene HCl Use for The Heart (RUTH) trial investigated the effects of raloxifene HCl in postmenopausal women (average age = 67 years) with known heart disease or at high risk for a coronary event. The RUTH trial demonstrated an increase in mortality due to stroke for raloxifene HCl compared to placebo. The incidence of stroke mortality was 1.5 per 1,000 women per year for placebo versus 2.2 per 1,000 women per year for raloxifene HCl ($p=0.0499$). The incidence of stroke, myocardial infarction, hospitalized acute coronary syndrome, cardiovascular mortality, or overall mortality (all causes combined) was comparable for raloxifene HCl and placebo. It can therefore be concluded that raloxifene HCl has no effect on clinical cardiovascular outcomes, in spite of the observed changes in lipid profile measurements.

## DETAILED PHARMACOLOGY

### Animal Pharmacology

**Effects on Bone:** The effects of raloxifene HCl 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 HCl 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 HCl 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 HCl and estrogen were observed, with 17α-ethynyl estradiol more potent than raloxifene HCl. Serum and urinary biochemical markers of bone metabolism also showed that the effects of raloxifene HCl 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 HCl 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 HCl-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 HCl treatment on bone quality.

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

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

**Effects on the Cardiovascular System:** Raloxifene HCl produces other cardiovascular effects *in vitro* or in animal models. These include inhibition of endothelial cell activation, inhibition of smooth-muscle cell migration, and inhibition of intimal thickening in response to balloon injury in rats.

**Effects on the Uterus:** In estrogen deficient animals (rats, rabbits, monkeys) raloxifene HCl fails to produce estrogen-like stimulation of the uterus. While a small, non-dose-related 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 HCl 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 HCl is unique among selective estrogen receptor modulators in this regard. The ability of raloxifene HCl 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:** As might be expected, raloxifene HCl has no antiproliferative activity against nonestrogen-dependent mammary carcinoma lines, such as the androgen-sensitive Shionogi mouse mammary carcinoma.

## 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 HCl 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 HCl 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 HCl, 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 HCl. 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 HCl 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 HCl 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 HCl 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 HCl 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 HCl-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 HCl 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 HCl. In raloxifene HCl-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 HCl-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 HCl'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 granulosa/theca cell origin was observed in females given 279 mg/kg. Systemic exposure (AUC) of raloxifene HCl 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 granulosa/theca cell origin and benign tumours of epithelial cell origin. The female rodents in these studies were treated during their reproductive lives when their ovaries were functional and highly responsive to hormonal stimulation. 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 $\geq$ 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 HCl 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 HCl 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 HCl.

**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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## IMPORTANT: PLEASE READ

**PART III: CONSUMER INFORMATION**

**[Pr]TEVA-RALOXIFENE**
Raloxifene hydrochloride

This leaflet is part III of a three-part "Product Monograph"published when TEVA-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 TEVA-RALOXIFENE. Contact your doctor or pharmacist if you have any questions about the drug.

## ABOUT THIS MEDICATION

What the medication is used for:
TEVA-RALOXIFENE is used to treat or to prevent osteoporosis in postmenopausal women.

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 menopause or after removal of the ovaries because of the decrease in estrogens. A variety of risk factors may promote osteoporosis. 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

The greater the number of risk factors, the greater the probability of developing 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 supplements.
- Do not smoke.
- Exercise. Bones need exercise to stay strong and healthy. Consult your doctor about an exercise program suitable to you.
- 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 TEVA-RALOXIFENE to prevent or treat osteoporosis.

What it does:
TEVA-RALOXIFENE is a Selective Estrogen Receptor Modulator or SERM. TEVA-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 bone, either to prevent or treat osteoporosis.

When it should not be used:
Do not take TEVA-RALOXIFENE if:

- you have **not** passed menopause. TEVA-RALOXIFENE is for use only by women **after menopause**.
- **you are pregnant or could become pregnant. TEVA-RALOXIFENE could harm your unborn child**.
- **you are nursing a baby. It is not known if TEVA-RALOXIFENE passes into breast milk or what effect it might have on the baby**.
- you have or have had blood clots in the veins that required a doctor's treatment. This may include clots in the legs, lungs or eyes. Taking TEVA-RALOXIFENE may increase the risk of getting these blood clots.
- you are allergic to raloxifene HCl or any of the other ingredients in TEVA-RALOXIFENE listed in the "nonmedicinal ingredients" section below.

What the medicinal ingredient is:

raloxifene hydrochloride

What the nonmedicinal ingredients are:
colloidal anhydrous silica, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, polydextrose, povidone, pregelatinized starch and titanium dioxide.

What dosage form it comes in
Tablet 60 mg.

## WARNINGS AND PRECAUTIONS

Before starting TEVA-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 TEVA-RALOXIFENE is only for postmenopausal women.
- have had an allergic reaction to any medicine you have taken.
- are intolerant to lactose because TEVA-RALOXIFENE contains lactose.
- have or ever had liver problems.
- have or ever had blood clots in the veins that have required a doctor's treatment. If you take warfarin (blood thinner) or other coumarin derivatives, TEVA-RALOXIFENE may not be suitable for you. TEVA-RALOXIFENE 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 TEVA-RALOXIFENE.
- are currently on any other medications, prescription or non prescription.
- have had a stroke or have a history of other significant risk factors for stroke, such as "mini-stroke" (TIA/transient ischemic attack), or a type of irregular heartbeat (atrial fibrillation).

Being immobile for a long time can increase the risk of blood clots in the veins. TEVA-RALOXIFENE may add to this risk. If while taking TEVA-RALOXIFENE you plan to be immobile, such as staying in bed after surgery, or taking a long plane trip, you should stop taking TEVA-RALOXIFENE at least 3 days before, to reduce your risk of blood clots in the veins. When you are back on your feet, you may start taking TEVA-RALOXIFENE again (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**).

## INTERACTIONS WITH THIS MEDICATION

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

The effect of TEVA-RALOXIFENE is significantly reduced if taken with cholestyramine (products which contain cholestyramine include Questran®, Questran Light®, Alti-Cholestyramine Light, Novo Cholamine, Novo-Cholamine Light, PMS-Cholestryramine).

Therefore, you should not take cholestyramine while taking TEVA-RALOXIFENE.

It is not recommended that you combine TEVA-RALOXIFENE with hormone replacement therapy (ERT or HRT) since safety information is limited and no studies have been done to look at the effectiveness or safety of this combination.
You should always check with your doctor before taking any other medication.

## PROPER USE OF THIS MEDICATION

Usual dose:
Take one TEVA-RALOXIFENE 60 mg tablet, once-a-day, any time, with or without food. TEVA-RALOXIFENE comes in a 30-day blister pack that you start as soon as you fill your prescription.

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 TEVA-RALOXIFENE is dependent upon your taking it regularly. Therefore, you should keep taking TEVA-RALOXIFENE until your doctor advises you otherwise.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Missed Dose:

If you miss a day of TEVA-RALOXIFENE take one pill as soon as you remember and resume one tablet once daily. Do not take two doses at the same time.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

During clinical trials, some women did have mild side effects however most women did not find these side effects serious enough to stop taking raloxifene hydrochloride. The most common side effects of TEVA-RALOXIFENE are:

- hot flashes
- leg cramps

Another common side effect is f1u-like symptoms. Similar to estrogen replacements, TEVA-RALOXIFENE may increase the risk of blood clots in the veins. Although this is an uncommon side effect, if you experience any of the following unusual symptoms talk to your doctor immediately:

- redness, swelling, heat or pain in your calves and legs
- sudden chest pain or shortness of breath
- a sudden change in your vision

TEVA-RALOXIFENE is not associated with adverse effects on the uterus, breast, or mental function. Therefore, any unexplained uterine bleeding, breast enlargement, breast pain, change in mood or deterioration of mental 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 | |
| **Uncommon** | **Blood clots in the veins*** | | | ✓ |
| **Rare** | **Blood clots in the lungs*** | | | ✓ |
| **Rare** | **Stroke fatality**** | | | |

**** See "SIDE EFFECTS AND WHAT TO DO ABOUT THEM" for symptoms of blood clots in the veins. If you experience any of the listed symptoms talk to your doctor immediately.***

*****Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking TEVA-RALOXIFENE.***

***This is not a complete list of side effects. For any unexpected effects while taking TEVA-RALOXIFENE, contact your doctor or pharmacist.***

All medicines should be stored out of the reach of children. TEVA-RALOXIFENE should be stored in its original package at room temperature (between 15 to 30°C) in a dry place.

## REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

***NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:
1-800-268-4127 ext. 5005 (English);
1-877-777-9117 (French)
or druginfo@tevacanada.com

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