# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020815, S003

## PRINTED LABELING

Sept. 30, 1999

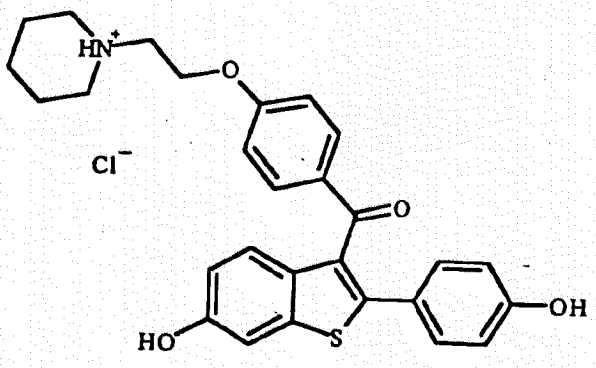


PV 3081-A AMP

# EVISTA®
## Raloxifene Hydrochloride
## 60 mg Tablets

### DESCRIPTION

EVISTA® (raloxifene hydrochloride) is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The chemical structure is:




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

EVISTA is supplied in a tablet dosage form for oral administration. Each EVISTA tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include anhydrous lactose, carnauba wax, crospovidone, FD&C Blue No. 2 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

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

Raloxifene's biological actions are largely mediated through binding to estrogen receptors. This binding results in activation of certain estrogenic pathways and blockade of others. Thus, raloxifene is a selective estrogen receptor modulator (SERM).

Raloxifene decreases resorption of bone and reduces biochemical markers of bone turnover to the premenopausal range. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, decreases in bone resorption based on radiocalcium kinetics studies, increases in bone mineral density (BMD) and decreases in incidence of fractures. Raloxifene also has effects on lipid metabolism. Raloxifene decreases total and LDL cholesterol levels but does not increase triglyceride levels. It does not change total HDL cholesterol levels. Preclinical data demonstrate that raloxifene is an estrogen antagonist in uterine and breast tissues. Clinical trial data (through a median of 42 months) suggest that EVISTA lacks estrogen-like effects on the uterus and breast tissue.

## 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 pharmacology studies in 292 postmenopausal women. Raloxifene exhibits high within-subject variability (approximately 30% coefficient of variation) of most pharmacokinetic parameters. Table 1 summarizes the pharmacokinetic parameters of raloxifene.

### 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 ($C_{max}$ 28% and AUC 16%), but does not lead to clinically meaningful changes in systemic exposure. EVISTA 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 (95%) bound to plasma proteins. Raloxifene binds to both albumin and $\alpha$1-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: raloxifene-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 portions of the plasma concentration curves 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 less than 0.2% is excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates.

**Table 1. Summary of raloxifene pharmacokinetic parameters in the healthy postmenopausal woman**

| | $C_{max}$[a] (ng/mL)/ (mg/kg) | $t_{½}$ (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: $C_{max}$ = maximum plasma concentration, $t_{½}$ = half-life, AUC = area under the curve, CL = clearance, V = volume of distribution, F = bioavailability, CV= coefficient of variation.

[a] Data normalized for dose in mg and body weight in kg.

[b] Range of observed half-life.

**Special Populations**

*Geriatric*--No differences in raloxifene pharmacokinetics were detected with regard to age (range 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 female and male 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; however, the influence of race cannot be conclusively determined.

*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 in women with estimated creatinine clearance as low as 21 mL/min are similar to women with normal creatinine clearance.

*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. 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).

**Drug-Drug Interactions**

Clinically significant drug-drug interactions are discussed in PRECAUTIONS.

*Ampicillin and Amoxicillin*--Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with coadministration of ampicillin. These reductions are consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected. Therefore, EVISTA can be concurrently administered with ampicillin. In the osteoporosis treatment trial, co-administration of amoxicillin had no discernable differences in plasma raloxifene concentrations.

*Antacids*--Concurrent administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene.

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

*Cholestyramine*--See PRECAUTIONS.

*Cyclosporine*--The coadministration of EVISTA with cyclosporine has not been evaluated.

*Digoxin*--Raloxifene has no effect on the pharmacokinetics of digoxin.

*Warfarin*--See PRECAUTIONS.

## Animal Pharmacology

The skeletal effects of raloxifene treatment were assessed in ovariectomized rats and monkeys. In rats, raloxifene prevented increased bone resorption and bone loss after ovariectomy. There were positive effects of raloxifene on bone strength, but the effects varied with time. Cynomolgus monkeys were treated with raloxifene or conjugated estrogens for 2 years. In terms of bone cycles, this is equivalent to approximately 6 years in humans. Raloxifene and estrogen suppressed bone turnover, and increased BMD in the lumbar spine and in the central cancellous bone of the proximal tibia. In this animal model, there was a positive correlation between vertebral compressive breaking force and BMD of the lumbar spine.

Histologic examination of bone from rats and monkeys treated with raloxifene showed no evidence of woven bone, marrow fibrosis, or mineralization defects.

These results are consistent with data from human studies of radiocalcium kinetics and markers of bone metabolism, and are consistent with EVISTA's action as a skeletal antiresorptive agent.

## Clinical Studies

In postmenopausal women with osteoporosis, EVISTA reduced the risk of vertebral fractures. EVISTA also increased BMD of the spine, hip and total body. Similarly, in early postmenopausal women without osteoporosis (women with normal or low BMD without fracture), EVISTA increased spine, hip and total body 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 EVISTA 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. All vertebral fractures were diagnosed radiographically; some of these fractures also were associated with symptoms (i.e., clinical fractures). 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.

EVISTA, 60 mg administered once daily, increased spine and hip BMD by 2-3%. EVISTA decreased the incidence of the first vertebral fracture from 4.3% for placebo to 1.9% for EVISTA (relative risk reduction = 55%) and subsequent vertebral fractures from 20.2% for placebo to 14.1% for EVISTA (relative risk reduction = 30%) (Table 2). All women in the study received calcium (500 mg/day) and vitamin D (400-600 IU/day). EVISTA reduced the incidence of vertebral fractures whether or not patients had a vertebral fracture upon study entry. The decrease in incidence of vertebral fracture was greater than could be accounted for by increase in BMD alone.

**Table 2. Effect of EVISTA on Risk of Vertebral Fractures**

| | Number of Patients | | Absolute Risk Reduction | Relative Risk Reduction (95% CI) |
|---|---|---|---|---|
| | EVISTA | Placebo | | |
| **Fractures diagnosed radiographically** | | | | |
| Patients with no baseline fracture[a] | n=1401 | n=1457 | | |
| Number (%) of patients with ≥1 new vertebral fracture | 27 (1.9%) | 62 (4.3%) | 2.4% | 55% (29%, 71%) |
| Patients with ≥1 baseline fracture[a] | n=858 | n=835 | | |
| Number (%) of patients with ≥1 new vertebral fracture | 121 (14.1%) | 169 (20.2%) | 6.1% | 30% (14%, 44%) |
| **Symptomatic vertebral fractures** | | | | |
| All randomized patients | n=2557 | n=2576 | | |
| Number (%) of patients with ≥1 new clinical (painful) vertebral fracture | 47 (1.8%) | 81 (3.1%) | 1.3% | 41% (17%, 59%) |

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

The mean percentage change in BMD from baseline for EVISTA was statistically significantly greater than for placebo at each skeletal site (Table 3).

**Table 3. EVISTA (60 mg once daily) related increases in BMD for the osteoporosis treatment study expressed as mean percentage increase versus placebo[ab]**

| | Time | | |
|---|---|---|---|
| | 12 Months | 24 Months | 36 Months |
| Site | % | % | % |
| 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 significant ($p<0.001$)

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

[b] All patients received calcium and vitamin D.

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 statistically significantly more frequent in the placebo group (3.7%) than in the EVISTA group (1.1%).

**Prevention of Osteoporosis**

The effects of EVISTA on BMD in postmenopausal women were examined in three 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). Women enrolled in these studies had a median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years postmenopause). The majority of the women were Caucasian (93.5%). Women were included if they had spine bone mineral density between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women. The mean T scores (number of standard deviations above or below the mean in healthy young women) for the 3 studies ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD. EVISTA, 60 mg administered once daily, produced 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. Compared with placebo, the increases in BMD for each of the 3 studies were statistically significant at 12 months and were maintained at 24 months (Table 4). The placebo groups lost approximately 1% of BMD over 24 months.

**Table 4. EVISTA (60 mg once daily) related increases in BMD for the three osteoporosis prevention studies expressed as mean percentage increase versus placebo[a] at 24 months[b]**

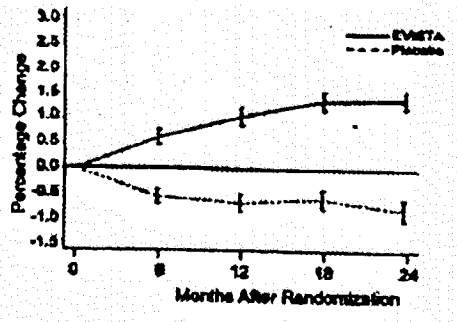
| | Study | | |
|---|---|---|---|
| Site | NA % | EU % | INT[c] % |
| Total Hip | 2.0 | 2.4 | 1.3 |
| Femoral Neck | 2.1 | 2.5 | 1.6 |
| Trochanter | 2.2 | 2.7 | 1.3 |
| Intertrochanter | 2.3 | 2.4 | 1.3 |
| Lumbar Spine | 2.0 | 2.4 | 1.8 |

Abbreviations: NA = North American, EU = European, INT = International.
Note: all BMD increases were significant ($p \leq 0.001$)

[a] All patients received calcium.
[b] Intent-to-treat analysis; last observation carried forward.
[c] All women in the study had previously undergone hysterectomy.

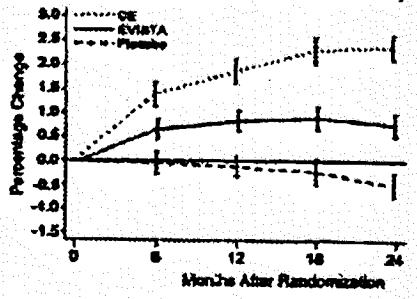
EVISTA also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's Triangle (hip) by 3.1% to 4.0%. The effects of EVISTA on forearm BMD were inconsistent between studies. In Study EU, EVISTA prevented bone loss at the ultradistal radius, whereas in Study NA, it did not.

Total hip mean percentage change from baseline
All placebo and EVISTA subjects 24-month data from Studies NA and EU[a]




[a] Intent to treat analysis, last observation carried forward

Total hip mean percentage change from baseline
All placebo, EVISTA, and CE subjects 24-month data from Study INT (hysterectomized women)[a]




CE = conjugated estrogens 0.625 mg/day
[a] Intent to treat analysis, last observation carried forward

**Assessments of Bone Turnover**

In a 31-week open-label radiocalcium kinetics study, 33 early postmenopausal women were randomized to treatment with once-daily EVISTA 60 mg, cyclic estrogen/progestin (0.625 mg conjugated estrogens daily with 5 mg medroxyprogesterone acetate daily for the first two weeks of each month [HRT]), or no treatment. Treatment with either EVISTA or HRT was associated with reduced bone resorption and a positive shift in calcium balance (-82 mg Ca/day and +60 mg Ca/day, respectively for EVISTA and -162 mg Ca/day and +91 mg Ca/day, respectively for HRT).

In both the osteoporosis treatment and prevention trials, EVISTA therapy resulted in consistent, statistically significant suppression of bone resorption and bone formation, 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.

**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 EVISTA-treated patients, there were statistically 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 histomorphometric evaluation of human iliac crest bone biopsies taken after administration of a fluorochrome substance to label areas of mineralizing bone. The effects of EVISTA on bone histomorphometry were determined by pre- and post-treatment biopsies in a 6-month study of Caucasian postmenopausal women who received once-daily doses of EVISTA 60 mg or 0.625 mg conjugated estrogens. Ten raloxifene-treated and 8 estrogen-treated women had evaluable bone biopsies at baseline and after 6 months of therapy. Bone formation rate/bone volume and activation frequency, the primary efficacy parameters, decreased to a greater extent with conjugated estrogen treatment versus EVISTA treatment, although the differences were not statistically significant. Bone in EVISTA- and estrogen-treated women showed no evidence of mineralization defects, woven bone, or marrow fibrosis.

**Effects on Lipid Metabolism**

The effects of EVISTA on selected lipid fractions and clotting factors were evaluated in a 6-month study of 390 postmenopausal women. EVISTA was compared with oral continuous combined estrogen/progestin (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate, [HRT]) and placebo (Table 5). EVISTA decreased serum total and LDL cholesterol without effects on serum total HDL cholesterol or triglycerides. In addition, EVISTA statistically significantly decreased serum fibrinogen and lipoprotein (a).

**Table 5. EVISTA (60 mg once daily) and oral HRT effects on selected lipid fractions and clotting factors in a 6-month study -- Median percentage change from baseline**

| | Treatment Group | | |
|---|---|---|---|
| Endpoint | EVISTA (N=95) % | HRT (N=96) % | PLACEBO (N=98) % |
| Total Cholesterol | -6.6[a] | -4.4[a] | 0.9 |
| LDL Cholesterol | -10.9[a] | -12.7[a] | 1.0 |
| HDL Cholesterol | 0.7[b] | 10.6[a] | 0.9 |
| HDL-2 Cholesterol | 15.4[b] | 33.3[a] | 0.0 |
| HDL-3 Cholesterol | -2.5[b] | 2.7 | 0.0 |
| Fibrinogen | -12.2[b] | -2.8 | -2.1 |
| Lipoprotein (a) | -4.1[b] | -16.3[a] | 3.3 |
| Triglycerides | -4.1[b] | 20.0[a] | -0.3 |
| Plasminogen Activator Inhibitor-1 | -2.1[b] | -29.0[a] | -9.4 |

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

[a] Significantly different from placebo ($p<0.05$).

[b] Significantly different from HRT ($p<0.05$).

Consistent with results from the 6-month study, in the osteoporosis treatment (36 months) and prevention (24 months) studies, EVISTA statistically significantly decreased serum total and LDL cholesterol by 5% to 6% and 8% to 10% respectively, compared to placebo. EVISTA did not affect HDL cholesterol or triglyceride levels. The effect of EVISTA-induced reductions in total and LDL cholesterol on risk for cardiovascular disease is currently under study.

**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. Placebo-treated women had a 0.27 mm mean decrease from baseline in endometrial thickness over 3 years, whereas the EVISTA-treated women had a 0.06 mm mean increase. Patients in the osteoporosis treatment study were not screened at baseline or excluded for pre-existing endometrial or uterine disease. This study was not specifically designed to detect endometrial polyps. Over the 36 months of the study, clinically or histologically benign endometrial polyps were reported in 17 of 1999 placebo-treated women, 37 of 1948 EVISTA-treated women and in 31 of 2010 women treated with raloxifene HCl 120 mg/day.

There was no difference between EVISTA- 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 total of 2978 TVU measurements were collected from 831 women in all dose groups. Placebo-treated women had a 0.04 mm mean increase from baseline in endometrial thickness over 2 years, whereas the EVISTA-treated women had a 0.09 mm mean increase. Endometrial thickness measurements in raloxifene-treated women were indistinguishable from placebo. There were no differences between the raloxifene and placebo groups with respect to the incidence of reported vaginal bleeding.

In a 6-month study of 18 postmenopausal women that compared EVISTA to conjugated estrogens (0.625 mg/day [ERT]), endpoint endometrial biopsies demonstrated stimulatory effects of ERT, which were not observed for EVISTA. All samples from EVISTA-treated women showed nonproliferative endometria.

A 12-month study of uterine effects compared a higher dose of raloxifene HCl (150 mg/day) with HRT. At baseline, 43 raloxifene-treated postmenopausal women and 37 HRT-treated women had a nonproliferative endometrium. At study completion, endometria 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.

Compared to placebo, EVISTA did not increase the risk of ovarian carcinoma.

**Effects on the Breast**

Across all placebo-controlled trials, EVISTA was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. EVISTA was associated with significantly less breast pain and tenderness than reported by women receiving estrogens with or without added progestin (see ADVERSE REACTIONS and Table 6).

Mammograms were routinely performed on an annual or biennial basis in all placebo-controlled clinical trials lasting at least 12 months. Independent review has determined that 25 cases (raloxifene and placebo combined) represented newly-diagnosed invasive breast cancer. Among 7108 women randomized to raloxifene, there were 10 cases of invasive breast cancer per 19,381 person-years of follow-up (0.52 per 1000). Among 3467 women randomized to placebo, there were 15 cases of invasive breast cancer per 9250 person-years of follow-up (1.62 per 1000). The effectiveness of raloxifene in reducing the risk of breast cancer has not been established.

## INDICATIONS AND USAGE

EVISTA 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).

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, 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.

## CONTRAINDICATIONS

EVISTA is contraindicated in lactating women or women who are or may become pregnant. EVISTA may cause fetal harm when administered to a pregnant woman. In rabbit studies, abortion and a low rate of fetal heart anomalies (ventricular septal defects) occurred in rabbits at doses ≥0.1 mg/kg (≥0.04 times the human dose based on surface area, $mg/m^2$), and hydrocephaly was observed in fetuses at doses ≥10 mg/kg (≥4 times the human dose based on surface area, $mg/m^2$). In rat studies, retardation of fetal development and developmental abnormalities (wavy ribs, kidney cavitation) occurred at doses ≥1 mg/kg (≥0.2 times the human dose based on surface area, $mg/m^2$). Treatment of rats at doses of 0.1 to 10 mg/kg (0.02 to 1.6 times the human dose based on surface area, $mg/m^2$) during gestation and lactation produced effects that included delayed and disrupted parturition; decreased neonatal survival and altered physical development; sex- and age-specific reductions in growth and changes in pituitary hormone content; and decreased lymphoid compartment size in offspring. At 10 mg/kg, raloxifene disrupted parturition which resulted in maternal and progeny death and morbidity. Effects in adult offspring (4 months of age) included uterine hypoplasia and reduced fertility; however, no ovarian or vaginal pathology was observed. The patient should be apprised of the potential hazard to