

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVISTA safely and effectively. See full prescribing information for EVISTA.

EVISTA (raloxifene hydrochloride) Tablet for Oral Use  
Initial U.S. Approval: 1997

### WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE

See full prescribing information for complete boxed warning.

- Increased risk of deep vein thrombosis and pulmonary embolism have been reported with EVISTA (5.1). Women with active or past history of venous thromboembolism should not take EVISTA (4.1).
- Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. Consider risk-benefit balance in women at risk for stroke (5.2, 14.5).

### RECENT MAJOR CHANGES

Boxed Warning	9/2007
Indications and Usage, Invasive Breast Cancer Risk Reduction (1)	9/2007
Warnings and Precautions, Death Due to Stroke (5.2)	7/2007
Warnings and Precautions, Cardiovascular Disease (5.3)	7/2007
Warnings and Precautions, Renal Impairment (5.8)	7/2007

### INDICATIONS AND USAGE

EVISTA® is an estrogen agonist/antagonist indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women. (1.1)
- Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. (1.2)
- Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer. (1.3)

Important Limitations: EVISTA is not indicated for the treatment of invasive breast cancer, reduction of the risk of recurrence of breast cancer, or reduction of risk of noninvasive breast cancer. (1.3)

### DOSAGE AND ADMINISTRATION

60 mg tablet orally once daily. (2.1)

### DOSAGE FORMS AND STRENGTHS

Tablets (not scored): 60 mg (3)

### CONTRAINDICATIONS

- Active or past history of venous thromboembolism, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. (4.1)

- Pregnancy, women who may become pregnant, and nursing mothers. (4.2, 8.1, 8.3)

### WARNINGS AND PRECAUTIONS

- *Venous Thromboembolism*: Increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. Discontinue use 72 hours prior to and during prolonged immobilization. (5.1, 6.1)
- *Death Due to Stroke*: Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. No increased risk of stroke was seen in this trial. Consider risk-benefit balance in women at risk for stroke. (5.2, 14.5)
- *Cardiovascular Disease*: EVISTA should not be used for the primary or secondary prevention of cardiovascular disease. (5.3, 14.5)
- *Premenopausal Women*: Use is not recommended. (5.4)
- *Hepatic Impairment*: Use with caution. (5.5)
- *Concomitant Use with Systemic Estrogens*: Not recommended. (5.6)
- *Hypertriglyceridemia*: If previous treatment with estrogen resulted in hypertriglyceridemia, monitor serum triglycerides. (5.7)

### ADVERSE REACTIONS

Adverse reactions (>2% and more common than with placebo) include: hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### DRUG INTERACTIONS

- *Cholestyramine*: Use with EVISTA is not recommended. Reduces the absorption and enterohepatic cycling of raloxifene. (7.1, 12.3)
- *Warfarin*: Monitor prothrombin time when starting or stopping EVISTA. (7.2, 12.3)
- *Highly Protein-Bound Drugs*: Use with EVISTA with caution. Highly protein-bound drugs include diazepam, diazoxide, and lidocaine. EVISTA is more than 95% bound to plasma proteins. (7.3, 12.3)

### USE IN SPECIFIC POPULATIONS

- *Pediatric Use*: Safety and effectiveness not established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2007

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66 \* Sections or subsections omitted from the full prescribing information are not listed.  
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## FULL PRESCRIBING INFORMATION

### **WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE**

- Increased risk of deep vein thrombosis and pulmonary embolism have been reported with EVISTA (5.1). Women with active or past history of venous thromboembolism should not take EVISTA (4.1).
- Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. Consider risk-benefit balance in women at risk for stroke (5.2, 14.5).

## **1 INDICATIONS AND USAGE**

### **1.1 Treatment and Prevention of Osteoporosis in Postmenopausal Women**

EVISTA is indicated for the treatment and prevention of osteoporosis in postmenopausal women [see *Clinical Studies (14.1, 14.2)*].

### **1.2 Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis**

EVISTA is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis [see *Clinical Studies (14.3)*].

### **1.3 Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women at High Risk of Invasive Breast Cancer**

EVISTA is indicated for the reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer [see *Clinical Studies (14.4)*].

The effect in the reduction in the incidence of breast cancer was shown in a study of postmenopausal women at high risk for breast cancer with a 5-year planned duration with a median follow-up of 4.3 years [see *Clinical Studies (14.4)*]. Twenty-seven percent of the participants received drug for 5 years. The long-term effects and the recommended length of treatment are not known.

High risk of breast cancer is defined as at least one breast biopsy showing lobular carcinoma in situ (LCIS) or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer  $\geq 1.66\%$  (based on the modified Gail model). Among the factors included in the modified Gail model are the following: current age, number of first-degree relatives with breast cancer, number of breast biopsies, age at menarche, nulliparity or age of first live birth. Healthcare professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-545-5979. Currently, no single clinical finding or test result can quantify risk of breast cancer with certainty.

After an assessment of the risk of developing breast cancer, the decision regarding therapy with EVISTA should be based upon an individual assessment of the benefits and risks.

EVISTA does not eliminate the risk of breast cancer. Patients should have breast exams and mammograms before starting EVISTA and should continue regular breast exams and mammograms in keeping with good medical practice after beginning treatment with EVISTA.

#### Important Limitations of Use for Breast Cancer Risk Reduction

- There are no data available regarding the effect of EVISTA on invasive breast cancer incidence in women with inherited mutations (BRCA1, BRCA2) to be able to make specific recommendations on the effectiveness of EVISTA.
- EVISTA is not indicated for the treatment of invasive breast cancer or reduction of the risk of recurrence.
- EVISTA is not indicated for the reduction in the risk of noninvasive breast cancer.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Recommended Dosing**

The recommended dosage is one 60 mg EVISTA tablet daily, which may be administered any time of day without regard to meals [see *Clinical Pharmacology (12.3)*].

For the indications in risk of invasive breast cancer the optimum duration of treatment is not known [see *Clinical Studies (14.3, 14.4)*].

### **2.2 Recommendations for Calcium and Vitamin D Supplementation**

For either osteoporosis treatment or prevention, supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits while daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and

125 kidney stones. The recommended intake of vitamin D is 400-800 IU daily. Patients at increased risk for vitamin D  
126 insufficiency (e.g., over the age of 70 years, nursing home bound, or chronically ill) may need additional vitamin D  
127 supplements. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D  
128 supplementation and measurement of 25-hydroxyvitamin D should be considered.

### 129 3 DOSAGE FORMS AND STRENGTHS

131 60 mg, white, elliptical, film-coated tablets (not scored). They are imprinted on one side with LILLY and the  
132 tablet code 4165 in edible blue ink.

### 133 4 CONTRAINDICATIONS

#### 134 4.1 Venous Thromboembolism

136 EVISTA is contraindicated in women with active or past history of venous thromboembolism (VTE),  
137 including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis [*see Warnings and Precautions*  
138 (5.1)].

#### 139 4.2 Pregnancy, Women Who May Become Pregnant, and Nursing Mothers

140 EVISTA is contraindicated in pregnancy, in women who may become pregnant, and in nursing mothers [*see*  
141 *Use in Specific Populations* (8.1, 8.3)]. EVISTA may cause fetal harm when administered to a pregnant woman. If  
142 this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be  
143 apprised of the potential hazard to the fetus.

144 In rabbit studies, abortion and a low rate of fetal heart anomalies (ventricular septal defects) occurred in  
145 rabbits at doses  $\geq 0.1$  mg/kg ( $\geq 0.04$  times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ), and hydrocephaly was  
146 observed in fetuses at doses  $\geq 10$  mg/kg ( $\geq 4$  times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ). In rat studies,  
147 retardation of fetal development and developmental abnormalities (wavy ribs, kidney cavitation) occurred at doses  
148  $\geq 1$  mg/kg ( $\geq 0.2$  times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ). Treatment of rats at doses of 0.1 to 10 mg/kg  
149 (0.02 to 1.6 times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ) during gestation and lactation produced effects that  
150 included delayed and disrupted parturition; decreased neonatal survival and altered physical development; sex- and  
151 age-specific reductions in growth and changes in pituitary hormone content; and decreased lymphoid compartment  
152 size in offspring. At 10 mg/kg, raloxifene disrupted parturition, which resulted in maternal and progeny death and  
153 morbidity. Effects in adult offspring (4 months of age) included uterine hypoplasia and reduced fertility; however,  
154 no ovarian or vaginal pathology was observed.

### 155 5 WARNINGS AND PRECAUTIONS

#### 156 5.1 Venous Thromboembolism

158 In clinical trials, EVISTA-treated women had an increased risk of venous thromboembolism (deep vein  
159 thrombosis and pulmonary embolism). Other venous thromboembolic events also could occur. A less serious event,  
160 superficial thrombophlebitis, also has been reported more frequently with EVISTA than with placebo. The greatest  
161 risk for deep vein thrombosis and pulmonary embolism occurs during the first 4 months of treatment, and the  
162 magnitude of risk appears to be similar to the reported risk associated with use of hormone therapy. Because  
163 immobilization increases the risk for venous thromboembolic events independent of therapy, EVISTA should be  
164 discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged  
165 bed rest), and EVISTA therapy should be resumed only after the patient is fully ambulatory. In addition, women  
166 taking EVISTA should be advised to move about periodically during prolonged travel. The risk-benefit balance  
167 should be considered in women at risk of thromboembolic disease for other reasons, such as congestive heart failure,  
168 superficial thrombophlebitis, and active malignancy [*see Contraindications* (4.1) and *Adverse Reactions* (6.1)].

#### 169 5.2 Death Due to Stroke

170 In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for  
171 coronary events, an increased risk of death due to stroke was observed after treatment with EVISTA. During an  
172 average follow-up of 5.6 years, 59 (1.2%) EVISTA-treated women died due to a stroke compared to 39 (0.8%)  
173 placebo-treated women (22 versus 15 per 10,000 women-years; hazard ratio 1.49; 95% confidence interval, 1.00-  
174 2.24;  $p=0.0499$ ). There was no statistically significant difference between treatment groups in the incidence of  
175 stroke (249 in EVISTA [4.9%] versus 224 placebo [4.4%]). EVISTA had no significant effect on all-cause  
176 mortality. The risk-benefit balance should be considered in women at risk for stroke, such as prior stroke or transient  
177 ischemic attack (TIA), atrial fibrillation, hypertension, or cigarette smoking [*see Clinical Studies* (14.5)].

#### 178 5.3 Cardiovascular Disease

EVISTA should not be used for the primary or secondary prevention of cardiovascular disease. In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, no cardiovascular benefit was demonstrated after treatment with raloxifene for 5 years [see *Clinical Studies (14.5)*].

#### 5.4 Premenopausal Use

There is no indication for premenopausal use of EVISTA. Safety of EVISTA in premenopausal women has not been established and its use is not recommended.

#### 5.5 Hepatic Impairment

EVISTA should be used with caution in patients with hepatic impairment. Safety and efficacy have not been established in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

#### 5.6 Concomitant Estrogen Therapy

The safety of concomitant use of EVISTA with systemic estrogens has not been established and its use is not recommended.

#### 5.7 History of Hypertriglyceridemia when Treated with Estrogens

Limited clinical data suggest that some women with a history of marked hypertriglyceridemia (>5.6 mmol/L or >500 mg/dL) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with EVISTA. Women with this medical history should have serum triglycerides monitored when taking EVISTA.

#### 5.8 Renal Impairment

EVISTA 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 [see *Clinical Pharmacology (12.3)*].

#### 5.9 History of Breast Cancer

EVISTA has not been adequately studied in women with a prior history of breast cancer.

#### 5.10 Use in Men

There is no indication for the use of EVISTA in men. EVISTA has not been adequately studied in men and its use is not recommended.

#### 5.11 Unexplained Uterine Bleeding

Any unexplained uterine bleeding should be investigated as clinically indicated. EVISTA-treated and placebo-treated groups had similar incidences of endometrial proliferation [see *Clinical Studies (14.1, 14.2)*].

#### 5.12 Breast Abnormalities

Any unexplained breast abnormality occurring during EVISTA therapy should be investigated. EVISTA does not eliminate the risk of breast cancer [see *Clinical Studies (14.4)*].

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to EVISTA in 8429 patients who were enrolled in placebo-controlled trials, including 6666 exposed for 1 year and 5685 for at least 3 years.

**Osteoporosis Treatment Clinical Trial (MORE)** — The safety of raloxifene in the treatment of osteoporosis was assessed in a large (7705 patients) multinational, placebo-controlled trial. Duration of treatment was 36 months, and 5129 postmenopausal women were exposed to raloxifene (2557 received 60 mg/day, and 2572 received 120 mg/day). The incidence of all-cause mortality was similar among groups: 23 (0.9%) placebo, 13 (0.5%) EVISTA-treated (raloxifene 60 mg), and 28 (1.1%) raloxifene 120 mg women died. Therapy was discontinued due to an adverse reaction in 10.9% of EVISTA-treated women and 8.8% of placebo-treated women.

**Venous Thromboembolism:** The most serious adverse reaction related to EVISTA was VTE (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis). During an average of study-drug exposure of 2.6 years, VTE occurred in about 1 out of 100 patients treated with EVISTA. Twenty-six EVISTA-treated women had a VTE compared to 11 placebo-treated women, the hazard ratio was 2.4 (95% confidence interval, 1.2, 4.5), and the highest VTE risk was during the initial months of treatment.

Common adverse reactions considered to be related to EVISTA therapy were hot flashes and leg cramps. Hot flashes occurred in about one in 10 patients on EVISTA and were most commonly reported during the first 6 months of treatment and were not different from placebo thereafter. Leg cramps occurred in about one in 14 patients on EVISTA.

234 Placebo-Controlled Osteoporosis Prevention Clinical Trials— The safety of raloxifene has been assessed  
 235 primarily in 12 Phase 2 and Phase 3 studies with placebo, estrogen, and estrogen-progestin therapy control groups.  
 236 The duration of treatment ranged from 2 to 30 months, and 2036 women were exposed to raloxifene (371 patients  
 237 received 10 to 50 mg/day, 828 received 60 mg/day, and 837 received from 120 to 600 mg/day).

238 Therapy was discontinued due to an adverse reaction in 11.4% of 581 EVISTA-treated women and 12.2% of  
 239 584 placebo-treated women. Discontinuation rates due to hot flashes did not differ significantly between EVISTA  
 240 and placebo groups (1.7% and 2.2%, respectively).

241 Common adverse reactions considered to be drug-related were hot flashes and leg cramps. Hot flashes  
 242 occurred in about one in four patients on EVISTA versus about one in six on placebo. The first occurrence of hot  
 243 flashes was most commonly reported during the first 6 months of treatment.

244 Table 1 lists adverse reactions occurring in either the osteoporosis treatment or in five prevention placebo-  
 245 controlled clinical trials at a frequency  $\geq 2.0\%$  in either group and in more EVISTA-treated women than in placebo-  
 246 treated women. Adverse reactions are shown without attribution of causality. The majority of adverse reactions  
 247 occurring during the studies were mild and generally did not require discontinuation of therapy.  
 248

249 **Table 1: Adverse Reactions Occurring in Placebo-Controlled Osteoporosis Clinical Trials at a**  
 250 **Frequency  $\geq 2.0\%$  and in More EVISTA-Treated (60 mg Once Daily) Women than Placebo-Treated Women<sup>a</sup>**

	Treatment		Prevention	
	EVISTA N=2557 %	Placebo N=2576 %	EVISTA N=581 %	Placebo N=584 %
<i>Body as a Whole</i>				
Infection	A	A	15.1	14.6
Flu Syndrome	13.5	11.4	14.6	13.5
Headache	9.2	8.5	A	A
Leg Cramps	7.0	3.7	5.9	1.9
Chest Pain	A	A	4.0	3.6
Fever	3.9	3.8	3.1	2.6
<i>Cardiovascular System</i>				
Hot Flashes	9.7	6.4	24.6	18.3
Migraine	A	A	2.4	2.1
Syncope	2.3	2.1	B	B
Varicose Vein	2.2	1.5	A	A
<i>Digestive System</i>				
Nausea	8.3	7.8	8.8	8.6
Diarrhea	7.2	6.9	A	A
Dyspepsia	A	A	5.9	5.8
Vomiting	4.8	4.3	3.4	3.3
Flatulence	A	A	3.1	2.4
Gastrointestinal Disorder	A	A	3.3	2.1
Gastroenteritis	B	B	2.6	2.1
<i>Metabolic and Nutritional</i>				
Weight Gain	A	A	8.8	6.8
Peripheral Edema	5.2	4.4	3.3	1.9
<i>Musculoskeletal System</i>				
Arthralgia	15.5	14.0	10.7	10.1
Myalgia	A	A	7.7	6.2
Arthritis	A	A	4.0	3.6
Tendon Disorder	3.6	3.1	A	A
<i>Nervous System</i>				
Depression	A	A	6.4	6.0
Insomnia	A	A	5.5	4.3
Vertigo	4.1	3.7	A	A
Neuralgia	2.4	1.9	B	B

Hypesthesia	2.1	2.0	B	B
<i>Respiratory System</i>				
Sinusitis	7.9	7.5	10.3	6.5
Rhinitis	10.2	10.1	A	A
Bronchitis	9.5	8.6	A	A
Pharyngitis	5.3	5.1	7.6	7.2
Cough Increased	9.3	9.2	6.0	5.7
Pneumonia	A	A	2.6	1.5
Laryngitis	B	B	2.2	1.4
<i>Skin and Appendages</i>				
Rash	A	A	5.5	3.8
Sweating	2.5	2.0	3.1	1.7
<i>Special Senses</i>				
Conjunctivitis	2.2	1.7	A	A
<i>Urogenital System</i>				
Vaginitis	A	A	4.3	3.6
Urinary Tract Infection	A	A	4.0	3.9
Cystitis	4.6	4.5	3.3	3.1
Leukorrhea	A	A	3.3	1.7
Uterine Disorder <sup>b,c</sup>	3.3	2.3	A	A
Endometrial Disorder <sup>b</sup>	B	B	3.1	1.9
Vaginal Hemorrhage	2.5	2.4	A	A
Urinary Tract Disorder	2.5	2.1	A	A

251 <sup>a</sup> A: Placebo incidence greater than or equal to EVISTA incidence; B: Less than 2% incidence and more frequent  
 252 with EVISTA.

253 <sup>b</sup> Includes only patients with an intact uterus: Prevention Trials: EVISTA, n=354, Placebo, n=364; Treatment Trial:  
 254 EVISTA, n=1948, Placebo, n=1999.

255 <sup>c</sup> Actual terms most frequently referred to endometrial fluid.  
 256

257 Comparison of EVISTA and Hormone Therapy — EVISTA was compared with estrogen-progestin therapy  
 258 in three clinical trials for prevention of osteoporosis. Table 2 shows adverse reactions occurring more frequently in  
 259 one treatment group and at an incidence  $\geq 2.0\%$  in any group. Adverse reactions are shown without attribution of  
 260 causality.  
 261

262 **Table 2: Adverse Reactions Reported in the Clinical Trials for Osteoporosis Prevention with EVISTA (60 mg**  
 263 **Once Daily) and Continuous Combined or Cyclic Estrogen Plus Progestin (Hormone Therapy) at an**  
 264 **Incidence  $\geq 2.0\%$  in any Treatment Group<sup>a</sup>**

	EVISTA (N=317) %	Hormone Therapy- Continuous Combined <sup>b</sup> (N=96) %	Hormone Therapy- Cyclic <sup>c</sup> (N=219) %
<i>Urogenital</i>			
Breast Pain	4.4	37.5	29.7
Vaginal Bleeding <sup>d</sup>	6.2	64.2	88.5
<i>Digestive</i>			
Flatulence	1.6	12.5	6.4
<i>Cardiovascular</i>			
Hot Flashes	28.7	3.1	5.9
<i>Body as a Whole</i>			
Infection	11.0	0	6.8
Abdominal Pain	6.6	10.4	18.7
Chest Pain	2.8	0	0.5

265 <sup>a</sup> These data are from both blinded and open-label studies.

266 <sup>b</sup> Continuous Combined Hormone Therapy = 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone  
 267 acetate.

268 <sup>c</sup> Cyclic Hormone Therapy = 0.625 mg conjugated estrogens for 28 days with concomitant 5 mg  
 269 medroxyprogesterone acetate or 0.15 mg norgestrel on Days 1 through 14 or 17 through 28.

270 <sup>d</sup> Includes only patients with an intact uterus: EVISTA, n=290; Hormone Therapy-Continuous Combined, n=67;  
 271 Hormone Therapy-Cyclic, n=217.

272  
 273 **Breast Pain** — Across all placebo-controlled trials, EVISTA was indistinguishable from placebo with regard  
 274 to frequency and severity of breast pain and tenderness. EVISTA was associated with less breast pain and tenderness  
 275 than reported by women receiving estrogens with or without added progestin.

276 **Gynecologic Cancers** — EVISTA-treated and placebo-treated groups had similar incidences of endometrial  
 277 cancer and ovarian cancer.

278 **Placebo-Controlled Trial of Postmenopausal Women at Increased Risk for Major Coronary Events (RUTH)**  
 279 — The safety of EVISTA (60 mg once daily) was assessed in a placebo-controlled multinational trial of 10,101  
 280 postmenopausal women (age range 55–92) with documented coronary heart disease (CHD) or multiple CHD risk  
 281 factors. Median study drug exposure was 5.1 years for both treatment groups [see *Clinical Studies (14.3)*]. Therapy  
 282 was discontinued due to an adverse reaction in 25% of 5044 EVISTA-treated women and 24% of 5057 placebo-  
 283 treated women. The incidence per year of all-cause mortality was similar between the raloxifene (2.07%) and  
 284 placebo (2.25%) groups.

285 Adverse reactions reported more frequently in EVISTA-treated women than in placebo-treated women  
 286 included peripheral edema (14.1% raloxifene versus 11.7% placebo), muscle spasms/leg cramps (12.1% raloxifene  
 287 versus 8.3% placebo), hot flashes (7.8% raloxifene versus 4.7% placebo), venous thromboembolic events (2.0%  
 288 raloxifene versus 1.4% placebo), and cholelithiasis (3.3% raloxifene versus 2.6% placebo) [see *Clinical Studies*  
 289 (14.3, 14.5)].

290 **Tamoxifen-Controlled Trial of Postmenopausal Women at Increased Risk for Invasive Breast Cancer (STAR)**  
 291 — The safety of EVISTA 60 mg/day versus tamoxifen 20 mg/day over 5 years was assessed in 19,747  
 292 postmenopausal women (age range 35–83 years) in a randomized, double-blind trial. As of 31 December 2005, the  
 293 median follow-up was 4.3 years. The safety profile of raloxifene was similar to that in the placebo-controlled  
 294 raloxifene trials [see *Clinical Studies (14.4)*].

## 295 **6.2 Postmarketing Experience**

296 Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible  
 297 to reliably estimate their frequency or establish a causal relationship to drug exposure.

298 Adverse reactions reported very rarely since market introduction include retinal vein occlusion, stroke, and  
 299 death associated with venous thromboembolism (VTE).



300

**301 7 DRUG INTERACTIONS****302 7.1 Cholestyramine**

303 Concomitant administration of cholestyramine with EVISTA is not recommended. Although not specifically  
304 studied, it is anticipated that other anion exchange resins would have a similar effect. EVISTA should not be co-  
305 administered with other anion exchange resins [see *Clinical Pharmacology (12.3)*].

**306 7.2 Warfarin**

307 If EVISTA is given concomitantly with warfarin or other warfarin derivatives, prothrombin time should be  
308 monitored more closely when starting or stopping therapy with EVISTA [see *Clinical Pharmacology (12.3)*].

**309 7.3 Other Highly Protein-Bound Drugs**

310 EVISTA should be used with caution with certain other highly protein-bound drugs such as diazepam,  
311 diazoxide, and lidocaine. Although not examined, EVISTA might affect the protein binding of other drugs.  
312 Raloxifene is more than 95% bound to plasma proteins [see *Clinical Pharmacology (12.3)*].

**313 7.4 Systemic Estrogens**

314 The safety of concomitant use of EVISTA with systemic estrogens has not been established and its use is not  
315 recommended.

**316 7.5 Other Concomitant Medications**

317 EVISTA can be concomitantly administered with ampicillin, amoxicillin, antacids, corticosteroids, and  
318 digoxin [see *Clinical Pharmacology (12.3)*].

319 The concomitant use of EVISTA and lipid-lowering agents has not been studied.

320

**321 8 USE IN SPECIFIC POPULATIONS****322 8.1 Pregnancy**

323 Pregnancy Category X. EVISTA should not be used in women who are or may become pregnant [see  
324 *Contraindications (4.2)*].

**325 8.3 Nursing Mothers**

326 EVISTA should not be used by lactating women [see *Contraindications (4.2)*]. It is not known whether this  
327 drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when  
328 raloxifene is administered to a nursing woman.

**329 8.4 Pediatric Use**

330 Safety and effectiveness in pediatric patients have not been established.

**331 8.5 Geriatric Use**

332 Of the total number of patients in placebo-controlled clinical studies of EVISTA, 61% were 65 and over,  
333 while 15.5% were 75 and over. No overall differences in safety or effectiveness were observed between these  
334 subjects and younger subjects, and other reported clinical experience has not identified differences in responses  
335 between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.  
336 Based on clinical trials, there is no need for dose adjustment for geriatric patients [see *Clinical Pharmacology*  
337 *(12.3)*].

**338 8.6 Renal Impairment**

339 EVISTA should be used with caution in patients with moderate or severe renal impairment [see *Warnings*  
340 *and Precautions (5.8) and Clinical Pharmacology (12.3)*].

**341 8.7 Hepatic Impairment**

342 EVISTA should be used with caution in patients with hepatic impairment [see *Warnings and Precautions*  
343 *(5.5) and Clinical Pharmacology (12.3)*].

344

**345 10 OVERDOSAGE**

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

348 In postmarketing spontaneous reports, raloxifene overdose has been reported very rarely (less than 1 out of  
349 10,000 [ $<0.01\%$ ] patients treated). The highest overdose has been approximately 1.5 grams. No fatalities associated  
350 with raloxifene overdose have been reported. Adverse reactions were reported in approximately half of the adults  
351 who took  $\geq 180$  mg raloxifene and included leg cramps and dizziness.

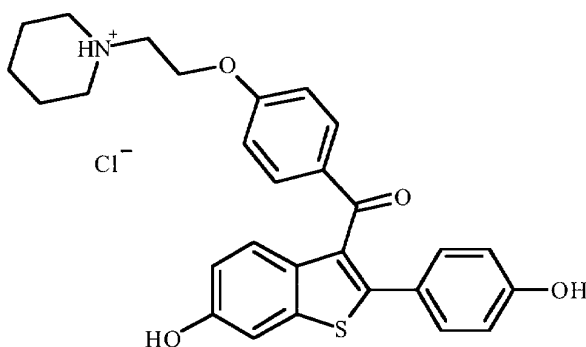
Two 18-month-old children each ingested raloxifene 180 mg. In these two children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhea, tremor, and flushing, as well as elevation in alkaline phosphatase.

There is no specific antidote for raloxifene.

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

## 11 DESCRIPTION

EVISTA (raloxifene hydrochloride) is an estrogen agonist/antagonist, commonly referred to as 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-piperidinyloxy)ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride (HCl) has the empirical formula C<sub>28</sub>H<sub>27</sub>NO<sub>4</sub>S•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, hypromellose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Raloxifene is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM). The biological actions of raloxifene are largely mediated through binding to estrogen receptors. This binding results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism). The agonistic or antagonistic action of raloxifene depends on the extent of recruitment of coactivators and corepressors to estrogen receptor (ER) target gene promoters.

Raloxifene appears to act as an estrogen agonist in bone. It decreases bone resorption and bone turnover, increases bone mineral density (BMD) and decreases fracture incidence. Preclinical data demonstrate that raloxifene is an estrogen antagonist in uterine and breast tissues. These results are consistent with findings in clinical trials, which suggest that EVISTA lacks estrogen-like effects on the uterus and breast tissue.

### 12.2 Pharmacodynamics

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.

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

395 of bone turnover (e.g., bone-specific alkaline phosphatase, osteocalcin, and collagen breakdown products). The  
 396 suppression of bone turnover markers was evident by 3 months and persisted throughout the 36-month and  
 397 24-month observation periods.

398 In a 31-week, open-label, radiocalcium kinetics study, 33 early postmenopausal women were randomized to  
 399 treatment with once-daily EVISTA 60 mg, cyclic estrogen/progestin (0.625 mg conjugated estrogens daily with  
 400 5 mg medroxyprogesterone acetate daily for the first 2 weeks of each month [hormone therapy]), or no treatment.  
 401 Treatment with either EVISTA or hormone therapy was associated with reduced bone resorption and a positive shift  
 402 in calcium balance (-82 mg Ca/day and +60 mg Ca/day, respectively, for EVISTA and -162 mg Ca/day and +91 mg  
 403 Ca/day, respectively, for hormone therapy).

404 There were small decreases in serum total calcium, inorganic phosphate, total protein, and albumin, which  
 405 were generally of lesser magnitude than decreases observed during estrogen or hormone therapy. Platelet count was  
 406 also decreased slightly and was not different from estrogen therapy.

### 407 12.3 Pharmacokinetics

408 The disposition of raloxifene has been evaluated in more than 3000 postmenopausal women in selected  
 409 raloxifene osteoporosis treatment and prevention clinical trials, using a population approach. Pharmacokinetic data  
 410 also were obtained in conventional pharmacology studies in 292 postmenopausal women. Raloxifene exhibits high  
 411 within-subject variability (approximately 30% coefficient of variation) of most pharmacokinetic parameters. Table 3  
 412 summarizes the pharmacokinetic parameters of raloxifene.

413 *Absorption* — Raloxifene is absorbed rapidly after oral administration. Approximately 60% of an oral dose is  
 414 absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is 2%. The  
 415 time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion  
 416 and enterohepatic cycling of raloxifene and its glucuronide metabolites.

417 Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene  
 418 ( $C_{max}$  28% and AUC 16%), but does not lead to clinically meaningful changes in systemic exposure. EVISTA can be  
 419 administered without regard to meals.

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

422 Raloxifene and the monoglucuronide conjugates are highly (95%) bound to plasma proteins. Raloxifene binds  
 423 to both albumin and  $\alpha$ 1-acid glycoprotein, but not to sex-steroid binding globulin.

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

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

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

438 *Excretion* — Raloxifene is primarily excreted in feces, and less than 0.2% is excreted unchanged in urine.  
 439 Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates.

440  
 441

**Table 3: Summary of Raloxifene Pharmacokinetic Parameters in the Healthy Postmenopausal Woman**

	$C_{max}^{a,b}$ (ng/mL)/ (mg/kg)	$t_{1/2}$ (hr) <sup>a</sup>	$AUC_{0-\infty}^{a,b}$ (ng•hr/mL)/ (mg/kg)	CL/F <sup>a</sup> (L/kg•hr)	V/F <sup>a</sup> (L/kg)
<i>Single Dose</i>					
Mean	0.50	27.7	27.2	44.1	2348
CV <sup>a</sup> (%)	52	10.7 to 273 <sup>c</sup>	44	46	52
<i>Multiple Dose</i>					
Mean	1.36	32.5	24.2	47.4	2853

	CV <sup>a</sup> (%)	37	15.8 to 86.6 <sup>c</sup>	36	41	56
442	<sup>a</sup> Abbreviations: C <sub>max</sub> = maximum plasma concentration, t <sub>1/2</sub> = half-life, AUC = area under the curve, CL =					
443	clearance, V = volume of distribution, F = bioavailability, CV = coefficient of variation.					
444	<sup>b</sup> Data normalized for dose in mg and body weight in kg.					
445	<sup>c</sup> Range of observed half-life.					
446						
447	<u>Special Populations</u>					
448	<i>Pediatric</i> — The pharmacokinetics of raloxifene has not been evaluated in a pediatric population [see Use in					
449	<i>Specific Populations (8.4)</i> ].					
450	<i>Geriatric</i> — No differences in raloxifene pharmacokinetics were detected with regard to age (range 42 to					
451	84 years) [see Use in <i>Specific Populations (8.5)</i> ].					
452	<i>Gender</i> — Total extent of exposure and oral clearance, normalized for lean body weight, are not significantly					
453	different between age-matched female and male volunteers.					
454	<i>Race</i> — Pharmacokinetic differences due to race have been studied in 1712 women, including 97.5% White,					
455	1.0% Asian, 0.7% Hispanic, and 0.5% Black in the osteoporosis treatment trial and in 1053 women, including					
456	93.5% White, 4.3% Hispanic, 1.2% Asian, and 0.5% Black in the osteoporosis prevention trials. There were no					
457	discernible differences in raloxifene plasma concentrations among these groups; however, the influence of race					
458	cannot be conclusively determined.					
459	<i>Renal Impairment</i> — In the osteoporosis treatment and prevention trials, raloxifene concentrations in women					
460	with mild renal impairment are similar to women with normal creatinine clearance. When a single dose of 120 mg					
461	raloxifene HCl was administered to 10 renally impaired males [7 moderate impairment (CrCl = 31 – 50 mL/min); 3					
462	severe impairment (CrCl ≤30 mL/min)] and to 10 healthy males (CrCl >80 mL/min), plasma raloxifene					
463	concentrations were 122% (AUC <sub>0-∞</sub> ) higher in renally impaired patients than those of healthy volunteers. Raloxifene					
464	should be used with caution in patients with moderate or severe renal impairment [see <i>Warnings and Precautions</i>					
465	<i>(5.8) and Use in Specific Populations (8.6)</i> ].					
466	<i>Hepatic Impairment</i> — The disposition of raloxifene was compared in 9 patients with mild (Child-Pugh Class					
467	A) hepatic impairment (total bilirubin ranging from 0.6 to 2 mg/dL) to 8 subjects with normal hepatic function					
468	following a single dose of 60 mg raloxifene HCl. Apparent clearance of raloxifene was reduced 56% and the half-					
469	life of raloxifene was not altered in patients with mild hepatic impairment. Plasma raloxifene concentrations were					
470	approximately 150% higher than those in healthy volunteers and correlated with total bilirubin concentrations. The					
471	pharmacokinetics of raloxifene has not been studied in patients with moderate or severe hepatic impairment.					
472	Raloxifene should be used with caution in patients with hepatic impairment [see <i>Warnings and Precautions (5.5)</i>					
473	<i>and Use in Specific Populations (8.6)</i> ].					
474	<u>Drug Interactions</u>					
475	<i>Cholestyramine</i> — Cholestyramine, an anion exchange resin, causes a 60% reduction in the absorption and					
476	enterohepatic cycling of raloxifene after a single dose. Although not specifically studied, it is anticipated that other					
477	anion exchange resins would have a similar effect [see <i>Drug Interactions (7.1)</i> ].					
478	<i>Warfarin</i> — In vitro, raloxifene did not interact with the binding of warfarin. The concomitant administration					
479	of EVISTA and warfarin, a coumarin derivative, has been assessed in a single-dose study. In this study, raloxifene					
480	had no effect on the pharmacokinetics of warfarin. However, a 10% decrease in prothrombin time was observed in					
481	the single-dose study. In the osteoporosis treatment trial, there were no clinically relevant effects of warfarin co-					
482	administration on plasma concentrations of raloxifene [see <i>Drug Interactions (7.2)</i> ].					
483	<i>Other Highly Protein-Bound Drugs</i> — In the osteoporosis treatment trial, there were no clinically relevant					
484	effects of co-administration of other highly protein-bound drugs (e.g., gemfibrozil) on plasma concentrations of					
485	raloxifene. In vitro, raloxifene did not interact with the binding of phenytoin, tamoxifen, or warfarin (see above) [see					
486	<i>Drug Interactions (7.3)</i> ].					
487	<i>Ampicillin and Amoxicillin</i> — Peak concentrations of raloxifene and the overall extent of absorption are					
488	reduced 28% and 14%, respectively, with co-administration of ampicillin. These reductions are consistent with					
489	decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic					
490	exposure and the elimination rate of raloxifene were not affected. In the osteoporosis treatment trial, co-					
491	administration of amoxicillin had no discernible differences in plasma raloxifene concentrations [see <i>Drug</i>					
492	<i>Interactions (7.5)</i> ].					
493	<i>Antacids</i> — Concomitant administration of calcium carbonate or aluminum and magnesium hydroxide-					
494	containing antacids does not affect the systemic exposure of raloxifene [see <i>Drug Interactions (7.5)</i> ].					
495	<i>Corticosteroids</i> — The chronic administration of raloxifene in postmenopausal women has no effect on the					
496	pharmacokinetics of methylprednisolone given as a single oral dose [see <i>Drug Interactions (7.5)</i> ].					

497 *Digoxin* — Raloxifene has no effect on the pharmacokinetics of digoxin [*see Drug Interactions (7.5)*].  
498 *Cyclosporine* — Concomitant administration of EVISTA with cyclosporine has not been studied.  
499 *Lipid-Lowering Agents* — Concomitant administration of EVISTA with lipid-lowering agents has not been  
500 studied.

## 501 502 **13 NONCLINICAL TOXICOLOGY**

### 503 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

504 Carcinogenesis — In a 21-month carcinogenicity study in mice, there was an increased incidence of ovarian  
505 tumors in female animals given 9 to 242 mg/kg, which included benign and malignant tumors of granulosa/theca  
506 cell origin and benign tumors of epithelial cell origin. Systemic exposure (AUC) of raloxifene in this group was  
507 0.3 to 34 times that in postmenopausal women administered a 60 mg dose. There was also an increased incidence of  
508 testicular interstitial cell tumors and prostatic adenomas and adenocarcinomas in male mice given 41 or 210 mg/kg  
509 (4.7 or 24 times the AUC in humans) and prostatic leiomyoblastoma in male mice given 210 mg/kg.

510 In a 2-year carcinogenicity study in rats, an increased incidence in ovarian tumors of granulosa/theca cell  
511 origin was observed in female rats given 279 mg/kg (approximately 400 times the AUC in humans). The female  
512 rodents in these studies were treated during their reproductive lives when their ovaries were functional and  
513 responsive to hormonal stimulation.

514 Mutagenesis — Raloxifene HCl was not genotoxic in any of the following test systems: the Ames test for  
515 bacterial mutagenesis with and without metabolic activation, the unscheduled DNA synthesis assay in rat  
516 hepatocytes, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese  
517 hamster ovary cells, the in vivo sister chromatid exchange assay in Chinese hamsters, and the in vivo micronucleus  
518 test in mice.

519 Impairment of Fertility — When male and female rats were given daily doses  $\geq 5$  mg/kg ( $\geq 0.8$  times the  
520 human dose based on surface area,  $\text{mg}/\text{m}^2$ ) prior to and during mating, no pregnancies occurred. In male rats, daily  
521 doses up to 100 mg/kg (16 times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ) for at least 2 weeks did not affect  
522 sperm production or quality or reproductive performance. In female rats, at doses of 0.1 to 10 mg/kg/day (0.02 to  
523 1.6 times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ), raloxifene disrupted estrous cycles and inhibited ovulation.  
524 These effects of raloxifene were reversible. In another study in rats in which raloxifene was given during the  
525 preimplantation period at doses  $\geq 0.1$  mg/kg ( $\geq 0.02$  times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ), raloxifene  
526 delayed and disrupted embryo implantation, resulting in prolonged gestation and reduced litter size. The  
527 reproductive and developmental effects observed in animals are consistent with the estrogen receptor activity of  
528 raloxifene.

### 529 **13.2 Animal Toxicology and/or Pharmacology**

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

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

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

## 541 542 **14 CLINICAL STUDIES**

### 543 **14.1 Treatment of Postmenopausal Osteoporosis**

#### 544 Effect on Fracture Incidence

545 The effects of EVISTA on fracture incidence and BMD in postmenopausal women with osteoporosis were  
546 examined at 3 years in a large randomized, placebo-controlled, double-blind, multinational osteoporosis treatment  
547 trial (MORE). All vertebral fractures were diagnosed radiographically; some of these fractures also were associated  
548 with symptoms (i.e., clinical fractures). The study population consisted of 7705 postmenopausal women with  
549 osteoporosis as defined by: a) low BMD (vertebral or hip BMD at least 2.5 standard deviations below the mean  
550 value for healthy young women) without baseline vertebral fractures or b) one or more baseline vertebral fractures.

551 Women enrolled in this study had a median age of 67 years (range 31 to 80) and a median time since menopause of  
552 19 years.

553 Effect on Bone Mineral Density

554 EVISTA, 60 mg administered once daily, increased spine and hip BMD by 2 to 3%. EVISTA decreased the  
555 incidence of the first vertebral fracture from 4.3% for placebo to 1.9% for EVISTA (relative risk reduction = 55%)  
556 and subsequent vertebral fractures from 20.2% for placebo to 14.1% for EVISTA (relative risk reduction = 30%)  
557 (see Table 4). All women in the study received calcium (500 mg/day) and vitamin D (400 to 600 IU/day). EVISTA  
558 reduced the incidence of vertebral fractures whether or not patients had a vertebral fracture upon study entry. The  
559 decrease in incidence of vertebral fracture was greater than could be accounted for by increase in BMD alone.

560  
561

**Table 4: Effect of EVISTA on Risk of Vertebral Fractures**

	Number of Patients		Absolute Risk Reduction (ARR)	Relative Risk Reduction (95% CI)
	EVISTA	Placebo		
<b>Fractures diagnosed radiographically</b>				
Patients with no baseline fracture <sup>a</sup>	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 <sup>a</sup>	n=858	n=835		
Number (%) of patients with ≥1 new vertebral fracture	121 (14.1%)	169 (20.2%)	6.1%	30% (14%, 44%)
<b>Symptomatic vertebral fractures</b>				
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%)

562 <sup>a</sup> Includes all patients with baseline and at least one follow-up radiograph.

563

564 The mean percentage change in BMD from baseline for EVISTA was statistically significantly greater than  
565 for placebo at each skeletal site (see Table 5).

566

567 **Table 5: EVISTA- (60 mg Once Daily) Related Increases in BMD<sup>a</sup> for the Osteoporosis Treatment Study**  
568 **Expressed as Mean Percentage Increase vs. Placebo<sup>b,c</sup>**

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 <sup>d</sup>	2.2	ND <sup>d</sup>
Distal Radius	ND <sup>d</sup>	0.9	ND <sup>d</sup>
Total Body	ND <sup>d</sup>	1.1	ND <sup>d</sup>

569 <sup>a</sup> Note: all BMD increases were significant (p<0.001).

570 <sup>b</sup> Intent-to-treat analysis; last observation carried forward.

571 <sup>c</sup> All patients received calcium and vitamin D.

572 <sup>d</sup> ND = not done (total body and radius BMD were measured only at 24 months).

573

574 Discontinuation from the study was required when excessive bone loss or multiple incident vertebral fractures  
 575 occurred. Such discontinuation was statistically significantly more frequent in the placebo group (3.7%) than in the  
 576 EVISTA group (1.1%).

#### 577 Bone Histology

578 Bone biopsies for qualitative and quantitative histomorphometry were obtained at baseline and after 2 years  
 579 of treatment. There were 56 paired biopsies evaluable for all indices. In EVISTA-treated patients, there were  
 580 statistically significant decreases in bone formation rate per tissue volume, consistent with a reduction in bone  
 581 turnover. Normal bone quality was maintained; specifically, there was no evidence of osteomalacia, marrow  
 582 fibrosis, cellular toxicity, or woven bone after 2 years of treatment.

#### 583 Effect on Endometrium

584 Endometrial thickness was evaluated annually in a subset of the study population (1781 patients) for 3 years.  
 585 Placebo-treated women had a 0.27 mm mean decrease from baseline in endometrial thickness over 3 years, whereas  
 586 the EVISTA-treated women had a 0.06 mm mean increase. Patients in the osteoporosis treatment study were not  
 587 screened at baseline or excluded for pre-existing endometrial or uterine disease. This study was not specifically  
 588 designed to detect endometrial polyps. Over the 36 months of the study, clinically or histologically benign  
 589 endometrial polyps were reported in 17 of 1999 placebo-treated women, 37 of 1948 EVISTA-treated women, and in  
 590 31 of 2010 women treated with raloxifene HCl 120 mg/day. There was no difference between EVISTA- and  
 591 placebo-treated women in the incidences of endometrial carcinoma, vaginal bleeding, or vaginal discharge.

### 592 **14.2 Prevention of Postmenopausal Osteoporosis**

593 The effects of EVISTA on BMD in postmenopausal women were examined in three randomized, placebo-  
 594 controlled, double-blind osteoporosis prevention trials: (1) a North American trial enrolled 544 women; (2) a  
 595 European trial, 601 women; and (3) an international trial, 619 women who had undergone hysterectomy. In these  
 596 trials, all women received calcium supplementation (400 to 600 mg/day). Women enrolled in these trials had a  
 597 median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years  
 598 postmenopause). The majority of the women were White (93.5%). Women were included if they had spine BMD  
 599 between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women.  
 600 The mean T scores (number of standard deviations above or below the mean in healthy young women) for the  
 601 three trials ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD.  
 602 EVISTA, 60 mg administered once daily, produced increases in bone mass versus calcium supplementation alone,  
 603 as reflected by dual-energy x-ray absorptiometric (DXA) measurements of hip, spine, and total body BMD.

#### 604 Effect on Bone Mineral Density

605 Compared with placebo, the increases in BMD for each of the three studies were statistically significant at  
 606 12 months and were maintained at 24 months (*see* Table 6). The placebo groups lost approximately 1% of BMD  
 607 over 24 months.

609 **Table 6: EVISTA- (60 mg Once Daily) Related Increases in BMD<sup>a</sup> for the Three Osteoporosis Prevention**  
 610 **Studies Expressed as Mean Percentage Increase vs. Placebo<sup>b</sup> at 24 Months<sup>c</sup>**

Site	Study		
	NA <sup>d</sup> %	EU <sup>d</sup> %	INT <sup>d,e</sup> %
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

611 <sup>a</sup> Note: all BMD increases were significant ( $p \leq 0.001$ ).

612 <sup>b</sup> All patients received calcium.

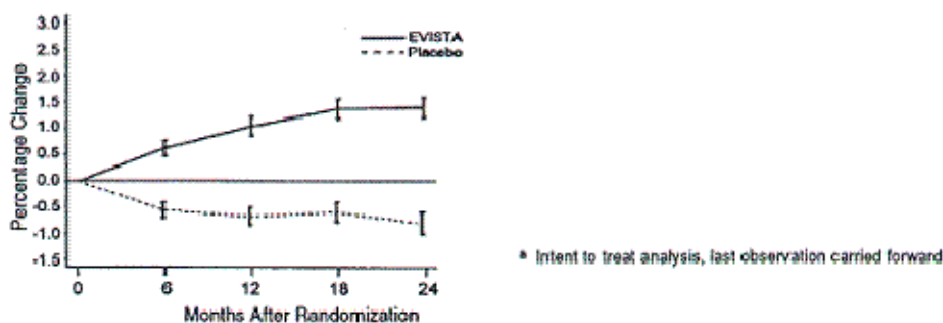
613 <sup>c</sup> Intent-to-treat analysis; last observation carried forward.

614 <sup>d</sup> Abbreviations: NA = North American, EU = European, INT = International.

615 <sup>e</sup> All women in the study had previously undergone hysterectomy.

616  
 617 EVISTA also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's  
 618 Triangle (hip) by 3.1% to 4.0%. The effects of EVISTA on forearm BMD were inconsistent between studies. In  
 619 Study EU, EVISTA prevented bone loss at the ultradistal radius, whereas in Study NA, it did not (*see* Figure 1).  
 620

Total hip mean percentage change from baseline  
All placebo and EVISTA subjects 24-month data from Studies NA and EU<sup>a</sup>



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

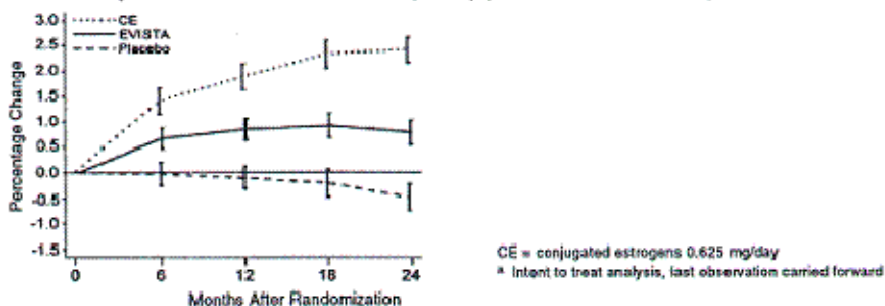


Figure 1: Total hip bone mineral density mean percentage change from baseline

#### Effect on Endometrium

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.

#### 14.3 Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis

##### MORE Trial

The effect of EVISTA on the incidence of breast cancer was assessed as a secondary safety endpoint in a randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial in postmenopausal women [see *Clinical Studies (14.1)*]. After 4 years, EVISTA, 60 mg administered once daily, reduced the incidence of all breast cancers by 62%, compared with placebo (HR 0.38, 95% CI 0.22-0.67). EVISTA reduced the incidence of invasive breast cancer by 71%, compared with placebo (ARR 3.1 per 1000 women-years); this was primarily due to an 80% reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo. Table 7 presents efficacy and selected safety outcomes.

##### CORE Trial

The effect of EVISTA on the incidence of invasive breast cancer was evaluated for 4 additional years in a follow-up study conducted in a subset of postmenopausal women originally enrolled in the MORE osteoporosis treatment trial. Women were not re-randomized; the treatment assignment from the osteoporosis treatment trial was carried forward to this study. EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 56%, compared with placebo (ARR 3.0 per 1000 women-years); this was primarily due to a 63%



646 reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo.  
647 There was no reduction in the incidence of ER-negative breast cancer. In the osteoporosis treatment trial and the  
648 follow-up study, there was no difference in incidence of noninvasive breast cancer between the EVISTA and  
649 placebo groups. Table 7 presents efficacy and selected safety outcomes.

650 In a subset of postmenopausal women followed for up to 8 years from randomization in MORE to the end of  
651 CORE, EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 60% in women  
652 assigned EVISTA (N=1355) compared with placebo (N=1286) (HR 0.40, 95% CI 0.21, 0.77; ARR 1.95 per 1000  
653 women-years); this was primarily due to a 65% reduction in the incidence of ER-positive invasive breast cancer in  
654 the EVISTA group compared with placebo.

655

656 **Table 7: EVISTA (60 mg Once Daily) vs. Placebo on Outcomes in Postmenopausal Women with Osteoporosis**

Outcomes	MORE 4 years					CORE <sup>a</sup> 4 years				
	Placebo (N=2576)		EVISTA (N=2557)		HR (95% CI) <sup>b</sup>	Placebo (N=1286)		EVISTA (N=2725)		HR (95% CI) <sup>b</sup>
	n	IR <sup>b</sup>	n	IR <sup>b</sup>		n	IR <sup>b</sup>	n	IR <sup>b</sup>	
Invasive <sup>c</sup> breast cancer	38	4.36	11	1.26	0.29 (0.15, 0.56) <sup>d</sup>	20	5.41	19	2.43	0.44 (0.24, 0.83) <sup>d</sup>
ER <sup>b,c</sup> positive	29	3.33	6	0.69	0.20 (0.08, 0.49)	15	4.05	12	1.54	0.37 (0.17, 0.79)
ER <sup>b,c</sup> negative	4	0.46	5	0.57	1.23 (0.33, 4.60)	3	0.81	6	0.77	0.95 (0.24, 3.79)
ER <sup>b,c</sup> unknown	5	0.57	0	0.00	N/A <sup>b</sup>	2	0.54	1	0.13	N/A <sup>b</sup>
Noninvasive <sup>c,e</sup> breast cancer	5	0.57	3	0.34	0.59 (0.14, 2.47)	2	0.54	5	0.64	1.18 (0.23, 6.07)
Clinical vertebral fractures	107	12.27	62	7.08	0.57 (0.42, 0.78)	N/A <sup>b</sup>	N/A <sup>b</sup>	N/A <sup>b</sup>	N/A <sup>b</sup>	N/A <sup>b</sup>
Death	36	4.13	23	2.63	0.63 (0.38, 1.07)	29	7.76	47	5.99	0.77 (0.49, 1.23)
Death due to stroke	6	0.69	3	0.34	0.49 (0.12, 1.98)	1	0.27	6	0.76	2.87 (0.35, 23.80)
Stroke	56	6.42	43	4.91	0.76 (0.51, 1.14)	14	3.75	49	6.24	1.67 (0.92, 3.03)
Deep vein thrombosis	8	0.92	20	2.28	2.50 (1.10, 5.68)	4	1.07	17	2.17	2.03 (0.68, 6.03)
Pulmonary embolism	4	0.46	11	1.26	2.76 (0.88, 8.67)	0	0.00	9	1.15	N/A <sup>b</sup>
Endometrial and uterine cancer <sup>f</sup>	5	0.74	5	0.74	1.01 (0.29, 3.49)	3	1.02	4	0.65	0.64 (0.14, 2.85)
Ovarian cancer	6	0.69	3	0.34	0.49 (0.12, 1.95)	2	0.54	2	0.25	0.47 (0.07, 3.36)
Hot flashes	151	17.31	237	27.06	1.61 (1.31, 1.97)	11	2.94	26	3.31	1.12 (0.55, 2.27)
Peripheral edema	134	15.36	164	18.73	1.23 (0.98, 1.54)	30	8.03	61	7.77	0.96 (0.62, 1.49)
Cholelithiasis	45	5.16	53	6.05	1.18 (0.79, 1.75)	12	3.21	35	4.46	1.39 (0.72, 2.67)

657 <sup>a</sup> CORE was a follow-up study conducted in a subset of 4011 postmenopausal women who originally enrolled in  
658 MORE. Women were not re-randomized; the treatment assignment from MORE was carried forward to this study.  
659 At CORE enrollment, the EVISTA group included 2725 total patients with 1355 patients who were originally  
660 assigned to raloxifene 60 mg once daily and 1370 patients who were originally assigned to raloxifene 120 mg at  
661 MORE randomization.

662 <sup>b</sup> Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = annual incidence rate per  
663 1000 women; N/A = not applicable.

664 <sup>c</sup> Included 1274 patients in placebo and 2716 patients in EVISTA who were not diagnosed with breast cancer prior  
665 to CORE enrollment.

666 <sup>d</sup>  $p < 0.05$ , obtained from the log-rank test, and not adjusted for multiple comparisons in MORE.

667 <sup>e</sup> All cases were ductal carcinoma in situ.

668 <sup>f</sup> Only patients with an intact uterus were included (MORE: placebo = 1999, EVISTA = 1950; CORE: placebo =  
669 1008, EVISTA = 2138).  
670

671 RUTH Trial

672 The effect of EVISTA on the incidence of invasive breast cancer was assessed in a randomized, placebo-  
 673 controlled, double-blind, multinational study in 10,101 postmenopausal women at increased risk of coronary events.  
 674 Women in this study had a median age of 67.6 years (range 55–92) and were followed for a median of 5.6 years  
 675 (range 0.01–7.1). Eighty-four percent were White, 9.8% of women reported a first-degree relative with a history of  
 676 breast cancer, and 41.4% of the women had a 5-year predicted risk of invasive breast cancer  $\geq 1.66\%$ , based on the  
 677 modified Gail model.

678 EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 44% compared  
 679 with placebo [absolute risk reduction (ARR) 1.2 per 1000 women-years]; this was primarily due to a 55% reduction  
 680 in estrogen receptor (ER)-positive invasive breast cancer in the EVISTA group compared with placebo (ARR 1.2  
 681 per 1000 women-years). There was no reduction in ER-negative invasive breast cancer. Table 8 presents efficacy  
 682 and selected safety outcomes.

683 **Table 8: EVISTA (60 mg Once Daily) vs. Placebo on Outcomes in Postmenopausal Women at Increased Risk**  
 684 **for Major Coronary Events**  
 685

Outcomes	Placebo <sup>a</sup> (N=5057)		EVISTA <sup>a</sup> (N=5044)		HR (95% CI) <sup>b</sup>
	n	IR <sup>b</sup>	n	IR <sup>b</sup>	
Invasive breast cancer	70	2.66	40	1.50	0.56 (0.38, 0.83) <sup>c</sup>
ER <sup>b</sup> positive	55	2.09	25	0.94	0.45 (0.28, 0.72)
ER <sup>b</sup> negative	9	0.34	13	0.49	1.44 (0.61, 3.36)
ER <sup>b</sup> unknown	6	0.23	2	0.07	0.33 (0.07, 1.63)
Noninvasive <sup>d</sup> breast cancer	5	0.19	11	0.41	2.17 (0.75, 6.24)
Clinical vertebral fractures	97	3.70	64	2.40	0.65 (0.47, 0.89)
Death	595	22.45	554	20.68	0.92 (0.82, 1.03)
Death due to stroke	39	1.47	59	2.20	1.49 (1.00, 2.24)
Stroke	224	8.60	249	9.46	1.10 (0.92, 1.32)
Deep vein thrombosis	47	1.78	65	2.44	1.37 (0.94, 1.99)
Pulmonary embolism	24	0.91	36	1.35	1.49 (0.89, 2.49)
Endometrial and uterine cancer <sup>e</sup>	17	0.83	21	1.01	1.21 (0.64 - 2.30)
Ovarian cancer <sup>f</sup>	10	0.41	17	0.70	1.69 (0.78, 3.70)
Hot flashes	241	9.09	397	14.82	1.68 (1.43, 1.97)
Peripheral edema	583	22.00	706	26.36	1.22 (1.09, 1.36)
Cholelithiasis <sup>g</sup>	131	6.20	168	7.83	1.26 (1.01, 1.59)

686 <sup>a</sup> Note: There were a total of 76 breast cancer cases in the placebo group and 52 in the EVISTA group. For two  
 687 cases, one in each treatment group, invasive status was unknown.

688 <sup>b</sup> Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = annual incidence rate per  
 689 1000 women.

690 <sup>c</sup>  $p < 0.05$ , obtained from the log-rank test, after adjusting for the co-primary endpoint of major coronary events.

691 <sup>d</sup> All cases were ductal carcinoma in situ.

692 <sup>e</sup> Only patients with an intact uterus were included (placebo = 3882, EVISTA = 3900).

693 <sup>f</sup> Only patients with at least one ovary were included (placebo = 4606, EVISTA = 4559).

694 <sup>g</sup> Only patients with an intact gallbladder at baseline were included (placebo = 4111, EVISTA = 4144).

695  
 696 The effect of EVISTA in reducing the incidence of invasive breast cancer was consistent among women  
 697 above or below age 65 or with a 5-year predicted invasive breast cancer risk, based on the modified Gail model,  
 698  $< 1.66\%$ , or  $\geq 1.66\%$ .

#### 699 **14.4 Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women at High Risk of Invasive** 700 **Breast Cancer**

##### 701 STAR Trial

702 The effects of EVISTA 60 mg/day versus tamoxifen 20 mg/day over 5 years on reducing the incidence of  
 703 invasive breast cancer were assessed in 19,747 postmenopausal women in a randomized, double-blind trial  
 704 conducted in North America by the National Surgical Adjuvant Breast and Bowel Project and sponsored by the

705 National Cancer Institute. Women in this study had a mean age of 58.5 years (range 35–83), a mean 5-year predicted  
 706 invasive breast cancer risk of 4.03% (range 1.66–23.61%), and 9.1% had a history of lobular carcinoma in situ  
 707 (LCIS). More than 93% of participants were White. As of 31 December 2005, the median time of follow-up was 4.3  
 708 years (range 0.07–6.50 years).

709 EVISTA was not superior to tamoxifen in reducing the incidence of invasive breast cancer. The observed  
 710 incidence rates of invasive breast cancer were EVISTA 4.4 and tamoxifen 4.3 per 1000 women per year. The results  
 711 from a noninferiority analysis are consistent with EVISTA potentially losing up to 35% of the tamoxifen effect on  
 712 reduction of invasive breast cancer. The effect of each treatment on invasive breast cancer was consistent when  
 713 women were compared by baseline age, history of LCIS, history of atypical hyperplasia, 5-year predicted risk of  
 714 breast cancer by the modified Gail model, or the number of relatives with a history of breast cancer. Fewer  
 715 noninvasive breast cancers occurred in the tamoxifen group compared to the EVISTA group. Table 9 presents  
 716 efficacy and selected safety outcomes.

717  
 718 **Table 9: EVISTA (60 mg Once Daily) vs. Tamoxifen (20 mg Once Daily) on Outcomes in**  
 719 **Postmenopausal Women at Increased Risk for Invasive Breast Cancer**

Outcomes	EVISTA (N=9751)		Tamoxifen (N=9736)		RR (95% CI) <sup>a</sup>
	n	IR <sup>a</sup>	n	IR <sup>a</sup>	
Invasive breast cancer	173	4.40	168	4.30	1.02 (0.82, 1.27)
ER <sup>a</sup> positive	115	2.93	120	3.07	0.95 (0.73, 1.24)
ER <sup>a</sup> negative	52	1.32	46	1.18	1.12 (0.74, 1.71)
ER <sup>a</sup> unknown	6	0.15	2	0.05	2.98 (0.53, 30.21)
Noninvasive breast cancer <sup>b</sup>	83	2.12	60	1.54	1.38 (0.98, 1.95)
DCIS <sup>a</sup>	47	1.20	32	0.82	1.46 (0.91, 2.37)
LCIS <sup>a</sup>	29	0.74	23	0.59	1.26 (0.70, 2.27)
Uterine cancer <sup>c</sup>	23	1.21	37	1.99	0.61 (0.34, 1.05)
Endometrial hyperplasia <sup>c</sup>	17	0.90	100	5.42	0.17 (0.09, 0.28)
Hysterectomy <sup>c</sup>	92	4.84	246	13.25	0.37 (0.28, 0.47)
Ovarian cancer <sup>d</sup>	18	0.66	14	0.52	1.27 (0.60, 2.76)
Ischemic heart disease <sup>e</sup>	138	3.50	125	3.19	1.10 (0.86, 1.41)
Stroke	54	1.36	56	1.42	0.96 (0.65, 1.42)
Deep vein thrombosis	67	1.69	92	2.35	0.72 (0.52, 1.00)
Pulmonary embolism	38	0.96	58	1.47	0.65 (0.42, 1.00)
Clinical vertebral fractures	58	1.46	58	1.47	0.99 (0.68, 1.46)
Cataracts <sup>f</sup>	343	10.34	435	13.19	0.78 (0.68, 0.91)
Cataract surgery <sup>f</sup>	240	7.17	295	8.85	0.81 (0.68, 0.96)
Death	104	2.62	109	2.76	0.95 (0.72, 1.25)
Edema <sup>g</sup>	741	18.66	664	16.83	1.11 (1.00, 1.23)
Hot flashes	6748	169.91	7170	181.71	0.94 (0.90, 0.97)

720 <sup>a</sup> Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; ER = estrogen receptor; IR = annual  
 721 incidence rate per 1000 women; LCIS = lobular carcinoma in situ; RR = risk ratio for women in the EVISTA  
 722 group compared with those in the tamoxifen group.

723 <sup>b</sup> Of the 60 noninvasive breast cases in the tamoxifen group, 5 were mixed types. Of the 83 noninvasive breast  
 724 cancers in the raloxifene group, 7 were mixed types.

725 <sup>c</sup> Only patients with an intact uterus at baseline were included (tamoxifen = 4739, EVISTA = 4715).

726 <sup>d</sup> Only patients with at least one intact ovary at baseline were included (tamoxifen = 6813, EVISTA = 6787).

727 <sup>e</sup> Defined as myocardial infarction, severe angina, or acute ischemic syndromes.

728 <sup>f</sup> Only patients who were free of cataracts at baseline were included (tamoxifen = 8342; EVISTA = 8333).

729 <sup>g</sup> Peripheral edema events are included in the term edema.

730  
 731

#### 14.5 Effects on Cardiovascular Disease

732 In a randomized, placebo-controlled, double-blind, multinational clinical trial (RUTH) of 10,101  
 733 postmenopausal women with documented coronary heart disease or at increased risk for coronary events, no  
 734 cardiovascular benefit was demonstrated after treatment with EVISTA 60 mg once daily for a median follow-up of  
 735 5.6 years. No significant increase or decrease was observed for coronary events (death from coronary causes,  
 736 nonfatal myocardial infarction, or hospitalization for an acute coronary syndrome). An increased risk of death due to  
 737 stroke after treatment with EVISTA was observed: 59 (1.2%) EVISTA-treated women died due to a stroke  
 738 compared to 39 (0.8%) placebo-treated women (2.2 versus 1.5 per 1000 women-years; hazard ratio 1.49; 95%  
 739 confidence interval, 1.00-2.24; p=0.0499). The incidence of stroke did not differ significantly between treatment  
 740 groups (249 with EVISTA [4.9%] versus 224 with placebo [4.4%]; hazard ratio 1.10; 95% confidence interval 0.92-  
 741 1.32; p=0.30; 9.5 versus 8.6 per 1000 women-years) [*see Warnings and Precautions (5.2, 5.3)*].  
 742

## 743 16 HOW SUPPLIED/STORAGE AND HANDLING

### 744 16.1 How Supplied

745 EVISTA 60 mg tablets are white, elliptical, and film coated. They are imprinted on one side with LILLY and  
 746 the tablet code 4165 in edible blue ink. They are available as follows:  
 747

Bottle (count)	NDC Number
30 (unit of use)	NDC 0002-4165-30
100 (unit of use)	NDC 0002-4165-02
2000	NDC 0002-4165-07

748

### 749 16.2 Storage and Handling

750 Store at controlled room temperature, 20° to 25°C (68° to 77°F) [*see USP*]. The USP defines controlled room  
 751 temperature as a temperature maintained thermostatically that encompasses the usual and customary working  
 752 environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more  
 753 than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies,  
 754 hospitals, and warehouses.  
 755

## 756 17 PATIENT COUNSELING INFORMATION

757 *See FDA-approved Medication Guide.*

758 Physicians should instruct their patients to read the Medication Guide before starting therapy with EVISTA  
 759 and to reread it each time the prescription is renewed.

### 760 17.1 Osteoporosis Recommendations, Including Calcium and Vitamin D Supplementation

761 For osteoporosis treatment or prevention, patients should be instructed to take supplemental calcium and/or  
 762 vitamin D if intake is inadequate. Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70  
 763 years, nursing home bound, chronically ill, or with gastrointestinal malabsorption syndromes) should be instructed  
 764 to take additional vitamin D if needed. Weight-bearing exercises should be considered along with the modification  
 765 of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.  
 766

### 767 17.2 Patient Immobilization

768 EVISTA should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-  
 769 surgical recovery, prolonged bed rest), and patients should be advised to avoid prolonged restrictions of movement  
 770 during travel because of the increased risk of venous thromboembolic events [*see Warnings and Precautions (5.1)*].

### 771 17.3 Hot Flashes or Flushes

772 EVISTA may increase the incidence of hot flashes and is not effective in reducing hot flashes or flushes  
 773 associated with estrogen deficiency. In some asymptomatic patients, hot flashes may occur upon beginning EVISTA  
 774 therapy.

### 775 17.4 Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis or at High Risk of Invasive Breast Cancer

776 Use of EVISTA is associated with the reduction of the risk of invasive breast cancer in postmenopausal  
 777 women. EVISTA has not been shown to reduce the risk of noninvasive breast cancer. When considering treatment,  
 778 physicians need to discuss the potential benefits and risks of EVISTA treatment with the patient.

779 EVISTA is not indicated for the treatment of invasive breast cancer or reduction of the risk of recurrence.

780 Patients should have breast exams and mammograms before starting EVISTA and should continue regular  
781 breast exams and mammograms in keeping with good medical practice after beginning treatment with EVISTA.  
782

783 Literature revised September DD, 2007

784 **Eli Lilly and Company**  
785 **Indianapolis, IN 46285, USA**  
786

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## Medication Guide

# EVISTA<sup>®</sup> (Ē-VISS-tah) (raloxifene hydrochloride) Tablets for Oral Use

6 Read the Medication Guide that comes with EVISTA before you start taking it and each time  
7 you refill your prescription. The information may have changed. This Medication Guide does not  
8 take the place of talking with your doctor about your medical condition or treatment. Talk with  
9 your doctor about EVISTA when you start taking it and at regular checkups.

### 10 **What is the most important information I should know about EVISTA?**

11 Serious and life-threatening side effects can occur while taking EVISTA. These include  
12 blood clots and dying from stroke:

- 13 • Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary  
14 embolism) have been reported with EVISTA. Women who have or have had blood clots  
15 in the legs, lungs, or eyes should not take EVISTA.
- 16 • Women who have had a heart attack or are at risk for a heart attack may have an  
17 increased risk of dying from stroke when taking EVISTA.

1. Before starting EVISTA, tell your doctor if you have had blood clots in your legs, lungs,  
or eyes, a stroke, mini-stroke (transient ischemic attack), or have an irregular heartbeat.

2. Stop taking EVISTA and call your doctor if you have:

- 18 • leg pain or a feeling of warmth in the lower leg (calf).
- 19 • swelling of the legs, hands, or feet.
- 20 • sudden chest pain, shortness of breath, or coughing up blood.
- 21 • sudden change in your vision, such as loss of vision or blurred vision.

3. Being still for a long time (such as sitting still during a long car or airplane trip or being in  
bed after surgery) can increase your risk of blood clots. (See **“What should I avoid if I  
am taking EVISTA?”**)

### 22 **What is EVISTA?**

23 EVISTA is a type of prescription medicine called a Selective Estrogen Receptor Modulator  
24 (SERM). EVISTA is for women after menopause, and has more than one use:

- 25 • **Osteoporosis:** EVISTA treats and prevents osteoporosis by helping make your bones  
26 stronger and less likely to break.
- 27 • **Invasive Breast Cancer:** If you have osteoporosis or are at high risk for breast cancer,  
28 EVISTA can be used to lower your chance of getting invasive breast cancer. EVISTA will  
29 not totally get rid of your chance of getting breast cancer. Your doctor can estimate your  
30 risk of breast cancer by asking you about risk factors, including:
- 31 • your age (getting older).
- 32 • family history of breast cancer in your mother, sister, or daughter.
- 33 • a history of any breast biopsy, especially an abnormal biopsy.

34 You and your doctor should talk about whether the possible benefit of EVISTA in  
35 lowering your chance of getting invasive breast cancer is greater than its possible risks.

36 EVISTA is not for use in premenopausal women (women who have not passed menopause).

### 37 **Who should not take EVISTA?**

38 Do not take EVISTA if you:

- 39 • have or have had blood clots in your legs, lungs, or eyes. Taking EVISTA may increase  
40 the risk of getting blood clots.
- 41 • are pregnant or could become pregnant. EVISTA could harm your unborn child.
- 42 • are nursing a baby. It is not known if EVISTA passes into breast milk or what effect it  
43 might have on the baby.

### 44 **What should I tell my doctor before taking EVISTA?**

45 EVISTA may not be right for you. Before taking EVISTA, tell your doctor about all your  
46 medical conditions, including if you:

- 47 • have had blood clots in your legs, lungs, or eyes, a stroke, mini-stroke (TIA/transient  
48 ischemic attack), or a type of irregular heartbeat (atrial fibrillation).
- 49 • have had breast cancer. EVISTA has not been fully studied in women who have a history  
50 of breast cancer.
- 51 • have liver or kidney problems.
- 52 • have taken estrogen in the past and had a high increase of triglycerides (a kind of fat in the  
53 blood).
- 54 • are pregnant, planning to become pregnant, or breast-feeding (see **“Who should not take  
55 EVISTA?”**).

56 Tell your doctor about all medicines you take, including prescription and non-prescription  
57 medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them  
58 and show it to your doctor and pharmacist each time you get a new medicine. Especially tell your  
59 doctor if you take\*:

- 60 • warfarin (Coumadin<sup>®</sup>, Jantoven<sup>®</sup>)



61 If you are taking warfarin or other coumarin blood thinners, your doctor may need to do a  
62 blood test when you first start or if you need to stop taking EVISTA. Names for this test  
63 include “prothrombin time,” “pro-time,” or “INR.” Your doctor may need to adjust the  
64 dose of your warfarin or other coumarin blood thinner.  
65

66 • cholestyramine

67 • estrogens

68 EVISTA should not be taken with cholestyramine or estrogens.

### 69 **How should I take EVISTA?**

70 • Take EVISTA exactly how your doctor tells you to.

71 • Keep taking EVISTA for as long as your doctor prescribes it for you. It is not known how  
72 long you should keep taking EVISTA to lower your chance of getting invasive breast  
73 cancers.

74 • It is important to get your refills on time so you do not run out of the medicine.

75 • Take one EVISTA tablet each day.

76 • Take EVISTA at any time of the day, with or without food.

77 • To help you remember to take EVISTA, it may be best to take it at about the same time  
78 each day.

79 • Calcium and vitamin D may be taken at the same time as EVISTA. It is important to take  
80 calcium and vitamin D, as directed by your physician, to prevent or treat osteoporosis.

81 • If you miss a dose, take it as soon as you remember. However, if it is almost time for your  
82 next dose, skip the missed dose and take only your next regularly scheduled dose. Do not  
83 take two doses at the same time.

### 84 **What should I avoid while taking EVISTA?**

85 • Being still for a long time (such as during long trips or being in bed after surgery) can  
86 increase the risk of blood clots. EVISTA may add to this risk. If you will need to be still  
87 for a long time, talk with your doctor about ways to reduce the risk of blood clots. On long  
88 trips, move around periodically. Stop taking EVISTA at least 3 days before a planned  
89 surgery or before you plan on being still for a long time. You should start taking EVISTA  
90 again when you return to your normal activities.

91 • Some medicines should not be taken with EVISTA (see **“What should I tell my doctor  
92 before taking EVISTA?”**).

93 **What are the possible side effects of EVISTA?**

94

95 Serious and life-threatening side effects can occur while taking EVISTA. These include blood  
96 clots and dying from stroke:

97 • Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary  
98 embolism) have been reported with EVISTA. Women who have or have had blood clots  
99 in the legs, lungs, or eyes should not take EVISTA.

100 • Women who have had a heart attack or are at risk for a heart attack may have an  
101 increased risk of dying from stroke when taking EVISTA.

102 See **“What is the most important information I should know about EVISTA?”**

103 The most common side effects of EVISTA are hot flashes, leg cramps, swelling of the feet,  
104 ankles, and legs, flu syndrome, joint pain, and sweating. Hot flashes are more common during  
105 the first 6 months after starting treatment.

106 These are not all the side effects of EVISTA. Tell your doctor about any side effect that  
107 bothers you or that does not go away. If you have any problems or questions that concern you  
108 while taking EVISTA, ask your doctor or pharmacist for more information.

109 **What else should I know about EVISTA?**

110 • Do not use EVISTA to prevent heart disease, heart attack, or strokes.

111 • To get the calcium and vitamin D you need, your doctor may advise you to change your  
112 diet and/or take supplemental calcium and vitamin D. Your doctor may suggest other ways  
113 to help treat or prevent osteoporosis, in addition to taking EVISTA and getting the calcium  
114 and vitamin D you need. These may include regular exercise, stopping smoking, and  
115 drinking less alcohol.

116 • Women who have hot flashes can take EVISTA. EVISTA does not treat hot flashes, and it  
117 may cause hot flashes in some women. (See **“What are the possible side effects of  
118 EVISTA?”**)

119 • EVISTA has not been found to cause breast tenderness or enlargement. If you notice any  
120 changes in your breasts, call your doctor to find out the cause. Before starting and while  
121 taking EVISTA you should have breast exams and mammograms, as directed by your  
122 doctor. Because EVISTA does not eliminate the chance of developing breast cancers, you  
123 need these examinations to find any breast cancers as early as possible.

124 • EVISTA should not cause spotting or menstrual-type bleeding. If you have any vaginal  
125 bleeding, call your doctor to find out the cause. EVISTA has not been found to increase  
126 the risk for cancer of the lining of the uterus.

127 • Women in clinical trials have taken EVISTA for up to eight years.

128 **How should I store EVISTA?**

- 129 • Store EVISTA at 68°F to 77°F (20°C-25°C).
- 130 • **Keep EVISTA and all medicines out of the reach of children.**

131 **General Information about the safe and effective use of EVISTA**

132 Medicines are sometimes prescribed for purposes other than those listed in a Medication  
133 Guide. Do not use EVISTA for a condition for which it was not prescribed. Do not give your  
134 EVISTA to other people, even if they have the same symptoms you have. It may harm them.

135 This Medication Guide is a summary of the most important information about EVISTA. If you  
136 would like more information about EVISTA, talk with your doctor. You can ask your doctor or  
137 pharmacist for information about EVISTA that is written for health professionals. For more  
138 information, call 1-800-545-5979 (toll-free) or go to the following website: [www.evista.com](http://www.evista.com).

139 **What are the ingredients in EVISTA?**

140 **Active Ingredient:** raloxifene hydrochloride

141 **Inactive Ingredients:** anhydrous lactose, carnauba wax, crospovidone, FD&C Blue No. 2  
142 aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, modified  
143 pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and  
144 titanium dioxide.

145  
146 This Medication Guide has been approved by the U.S. Food and Drug Administration.

147  
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