Application Number: 020815, S02

Trade Name: EVISTA TABLETS

Generic Name: RALOXIFENE HYDROCHLORIDE

Sponsor: ELI LILLY and COMPANY

Approval Date: 11/24/98

INDICATION(s): FOR THE PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
### CONTENTS

<table>
<thead>
<tr>
<th>Item</th>
<th>Included</th>
<th>Pending Completion</th>
<th>Not Prepared</th>
<th>Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tentative Approval Letter</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Approvable Letter</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Printed Labeling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EA/FONSI</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Biopharmaceutics Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Administrative/Correspondence Document(s)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020815, S02

APPROVAL LETTER
Eli Lilly & Company
Attention: Gregory Enas, Ph.D.
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:


We acknowledge receipt of your submissions dated August 28 and November 19, 1998. Supplemental application 002 provides for changes in the Effects on the Breast subsection of the CLINICAL PHARMACOLOGY section, and in the Additional Safety Information subsection of the ADVERSE REACTIONS section of the package insert.

We have completed the review of this supplemental application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated November 19, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on November 19, 1998.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-815/S-002." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301)827-6392.

Sincerely,

[Signature]

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-815
HFD-510/Div. Files
HFD-510/R.Hedin
HF-2/MedWatch (with labeling) + labeling review
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: /November 20, 1998
Initialed by:
final:
filename: N20815AP.LT3

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815, S02

PRINTED LABELING
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:

![Chemical Structure of Raloxifene]

The chemical designation is methoxybenzene, (6-hydroxy-2-(4-hydroxyphenyl)benzene)-3-y1-(4-[2-((1-piperidinyl)ethyl)oxy]pheny1)-hydrochloride. Raloxifene hydrochloride (HCl) has the empirical formula C_{45}H_{53}ClNO_2.S. HCl, which corresponds to a molecular weight of 510.0. 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 56.71 mg of free base. The inactive ingredients include anthranilic acid, camphor, FD&C Blue No. 2 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, modified pharmaceutical-grade polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action
Decreases in estrogen levels after oophorectomy or menopause lead to increases in bone resorption and bone loss. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive forces. This imbalance between resorption and formation is related to loss of estrogen, and may also involve age-related impairment of osteoblasts or their precursors.

Raloxifene reduces resorption of bone and decreases overall bone turnover. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, evidence from radiocarbon kinetics studies for decreased bone resorption and increases in bone mineral density (BMD). Raloxifene’s biologic actions, like those of estrogen, are mediated through binding to estrogen receptors. This binding results in differential expression of multiple estrogen-regulated genes in different tissues. Recent data suggest that the estrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.

Clinical data indicate that raloxifene, a selective estrogen receptor modulator (SERM), has estrogen-like effects on bone (increase in BMD) and on lipid (decrease in total and LDL cholesterol levels) metabolism. Preclinical data demonstrate that raloxifene is an estrogen antagonist in uterus and breast tissues. Preliminary clinical data (through 3 months) suggest EVISTA lacks estrogen-like effects on uterus and breast tissue.

Pharmacokinetics
The disposition of raloxifene has been evaluated in 275 postmenopausal women in conventional clinical pharmacology studies and in more than 1300 postmenopausal women in selected raloxifene trials. Raloxifene exhibits high within-subject variability (approximately 60% coefficient of variation) of its pharmacokinetic parameters. Table 1 summarizes the pharmacokinetic parameters of raloxifene.

Absorption
Raloxifene is absorbed rapidly following oral administration. Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is 20%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconverion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene (Cmax, 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 bound to plasma proteins. Raloxifene binds to both albumin and α1-acid glycoprotein, but not to sex steroid binding globulin. In vitro, raloxifene does not interact with the binding of warfarin, phenytoin, or tamoxifen to plasma proteins.

Metabolism
Biotransformation and disposition of raloxifene in humans have been determined following oral administration of 14C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: 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/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/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. In the osteoporosis prevention trials, raloxifene and metabolite concentrations are similar for women with estimated creatinine clearance as low as 23 mL/min.
Table 1. Summary of raclopride pharmacokinetic parameters in the healthy postmenopausal woman

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Dose</th>
<th>Multiple Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Mean (%)</td>
<td>0.90</td>
<td>0.69</td>
</tr>
<tr>
<td>tX (min)</td>
<td>27.7</td>
<td>21.5</td>
</tr>
<tr>
<td>Nt (hr)</td>
<td>0.52</td>
<td>0.47</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>44.1</td>
<td>46.2</td>
</tr>
<tr>
<td>AUCt (ng/ml/hr)</td>
<td>2384</td>
<td>2953</td>
</tr>
<tr>
<td>C0 (ng/ml)</td>
<td>27.2</td>
<td>24.2</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>52.4</td>
<td>56.5</td>
</tr>
<tr>
<td>C1/2 (ng/ml)</td>
<td>30.1</td>
<td>37.3</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>4.1</td>
<td>2.9</td>
</tr>
<tr>
<td>V1 (L/kg)</td>
<td>53.1</td>
<td>56.1</td>
</tr>
<tr>
<td>V2 (L/kg)</td>
<td>294</td>
<td>294</td>
</tr>
</tbody>
</table>

Adapted from: CV = coefficient of variation; tX = time to maximum concentration; n = number; C0 = plasma raclopride concentration at time 0; AUCt = area under the concentration-time curve; t1/2 = terminal half-life; V1 = volume of distribution in the vascular compartment; V2 = volume of distribution in the extravascular compartment.

Special Populations

Gender—No differences in raclopride pharmacokinetics were detected with regard to age (range 45 to 84 years).

Pediatric—The pharmacokinetics of raclopride have not been evaluated in a pediatric population.

Race—Pharmacokinetic differences due to race have not been reported. Total plasma raclopride concentrations were similar between Asian and Non-Asian patients.

Renal Insufficiency—Since negligible amounts of raclopride are eliminated in urine, a uric acid in patients with renal insufficiency was not conducted.

Hepatic Dysfunction—Racloride 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 raclopride concentrations were approximately 2.5 times higher in cirrhotics compared with normal controls.

Drug-Drug Interactions

Clinically significant drug-drug interactions are discussed in PRECAUTIONS. Continuous administration of calcium carbonate or aluminum/magnesium hydroxide-containing antacids does not affect the systemic exposure of raclopride.

Concomitant Use—The coadministration of EVISTA with corticosteroids has not been evaluated.

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

Digoxin—Racloride has no effect on the pharmacokinetics of digoxin.

Animal Pharmacology

The skeletal effects of raclopride treatment were assessed in ovariectomized rats and monkeys. Raclopride prevented increased bone resorption and bone loss after ovariectomy. These effects were dose-dependent and were observed in both rats and monkeys.

Clinical Studies

Effects on Total Body and Regional Bone Mineral Density

In postmenopausal women, EVISTA preserves bone mass and increases BMD relative to placebo alone at 24 months. The effects on hip bone mass are similar to that seen with the spine. The relationship of BMD changes to skeletal fracture rates have not yet been established in EVISTA-treated women.

The effects of EVISTA on BMD in postmenopausal women were examined in three large randomized, placebo-controlled, double-blind osteoporosis prevention trials: (1) a North American trial enrolled 544 women; (2) a European trial, 601 women; and (3) an International trial, 626 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 mean age of 54 years and a mean BMI of 25 kg/m². The majority of the women were Caucasian (93%). Women were also enrolled if they had a risk factor for hip fracture (e.g., history of hip fracture, low BMD at other sites, or other risk factors). The mean T scores (number of standard deviations above or below the mean for young women) for the 3 studies ranged from -1.01 to -2.74 for spine BMD and included both normal and low BMD. EVISTA, 60 mg administered daily, significantly increased bone in bone mineral density at 12 months, and the total body BMD. Compared with placebo, the increase in BMD for both the spine and total body BMD was statistically significant at 12 months and was maintained at 24 months.

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

<table>
<thead>
<tr>
<th>Site</th>
<th>NA %</th>
<th>EU %</th>
<th>INT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hip</td>
<td>2.0</td>
<td>2.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>2.1</td>
<td>2.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Trochanter</td>
<td>2.3</td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Intermuscular</td>
<td>2.4</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>2.1</td>
<td>2.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Adapted from: NA = North American; EU = European; INT = International. All women in the study had premenopausal osteoporosis treated for 12 months. EVISTA also increased BMD compared with placebo in the total body. 0.1% to 0.6% in the spine (T-scores) and 0.1% to 0.6% in the total body BMD. The effects of EVISTA in bone were consistent between studies. In Study EU, EVISTA prevented bone loss at the ultradistal radius, whereas in Study NA, it did not.
Assessments of Bone Turnover

In a 12-week, placebo-controlled, randomized, double-blind, parallel-group study, 248 postmenopausal women were randomized to receive either a daily oral dose of EVISTA 60 mg, an oral dose of estradiol 2 mg, or a placebo. The study was conducted in two phases. In the first phase, 120 women were randomized to receive EVISTA 60 mg, estradiol 2 mg, or placebo for 12 weeks. In the second phase, 128 women were randomized to receive EVISTA 60 mg or estradiol 2 mg for 12 weeks, while the placebo group remained unchanged.

Bone Histomorphometry

The bone biopsy specimens were evaluated for bone formation and bone resorption. The effects of EVISTA were compared to those of placebo. The results showed that EVISTA significantly decreased bone formation and increased bone resorption compared to placebo.

BMD Measurements

In both phases of the study, BMD measurements were performed at baseline and at 12 weeks. The results showed that EVISTA significantly increased BMD compared to placebo.

Lipid Metabolism

The effects of EVISTA on lipid metabolism were evaluated. The study showed that EVISTA significantly increased HDL cholesterol and decreased triglycerides compared to placebo.

Hormone Receptor Status

The hormone receptor status was evaluated in both phases of the study. The results showed that EVISTA significantly increased the expression of estrogen receptor (ER) compared to placebo.

Effects on the Uterus

In a 12-week study of 248 postmenopausal women, EVISTA significantly decreased the thickness of the endometrium compared to placebo.

In conclusion, EVISTA significantly improved bone health, increased BMD, improved lipid metabolism, and decreased the risk of endometrial cancer compared to placebo.

Table 3. EVISTA (60 mg daily) and oral HRT effects on selected lipid fractions and clotting factors in a 6-month study — Median percentage change from baseline

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EVISTA (N=96)</th>
<th>HRT (N=96)</th>
<th>PLACEBO (N=96)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>−0.2%</td>
<td>−4.4%</td>
<td>−3.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>−0.1%</td>
<td>−12.7%</td>
<td>−1.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>15.0%</td>
<td>33.3%</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−2.6%</td>
<td>−8.7%</td>
<td>−2.1%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fibrinogen (ng/mL)</td>
<td>−1.4%</td>
<td>−10.5%</td>
<td>−3.3%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Antithrombin Activating Inhibitor I</td>
<td>−4.1%</td>
<td>−20.0%</td>
<td>−6.3%</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Notes:
- Significant difference from placebo (p<0.05).
- No significant difference from placebo (p>0.05).

In the osteoporosis prevention studies (N=1754), 24-month data were consistent with results from the 6-month study. Compared to placebo, EVISTA significantly reduced the risk of fracture by approximately 30% and 7% respectively, but did not affect BMD, cholesterol or triglycerides.

In placebo-controlled osteoporosis prevention trials, endometrial thickness was evaluated every 6 months (for 24 months) by transvaginal ultrasonography (TVU). A total of 281 TVU measurements were collected from 831 women in all dose groups. Endometrial thickness in EVISTA-treated women was reduced to that of premenopausal women.

In a 12-month study of 248 postmenopausal women, EVISTA significantly increased BMD compared to placebo.

In conclusion, EVISTA significantly improved bone health, increased BMD, improved lipid metabolism, and decreased the risk of endometrial cancer compared to placebo.

**Pfizer Lillith Company, 1997, 1998**
Mammograms were routinely performed on an annual or biennial basis in all placebo-controlled clinical trials lasting at least 10 months. Independent review has determined that 16 cases (raloxifene and placebo combined) represented newly diagnosed invasive breast cancer. Among 7077 women randomized to raloxifene, there were 6 cases of invasive breast cancer per 14,603 person-years of follow-up (0.41 per 1000). Among 3388 women randomized to placebo, there were 10 cases of invasive breast cancer per 6991 person-years of follow-up (1.43 per 1000). The effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established.

INDICATIONS AND USAGE

RALOXIFENE is indicated for the prevention of osteoporosis in postmenopausal women.

The effects of RALOXIFENE on fracture risk are not yet known. The effects of RALOXIFENE on fracture risk are not yet known. The effects of RALOXIFENE on fracture risk are not yet known. The effects of RALOXIFENE on fracture risk are not yet known. The effects of RALOXIFENE on fracture risk are not yet known.

CONTRAINdications

RALOXIFENE is contraindicated in women who are or may become pregnant. RALOXIFENE is contraindicated in women who are or may become pregnant. RALOXIFENE is contraindicated in women who are or may become pregnant. RALOXIFENE is contraindicated in women who are or may become pregnant.

WARNINGS

Venous Thromboembolic Events—An analysis of RALOXIFENE-treated women across all placebo-controlled clinical trials showed an increased risk of venous thromboembolic events defined as deep vein thrombosis, pulmonary embolism, and fatal or nonfatal pulmonary embolism. The greatest risk for thromboembolic events occurs during the first 4 months of treatment. RALOXIFENE should be discontinued at least 12 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and RALOXIFENE therapy should be reserved only after the completion of mobilization. Patients should be advised to avoid prolonged recumbency or to limit activity during mobilization. The risk-benefit balance should be considered in patients taking RALOXIFENE. Risk-benefit balance should be considered in patients taking RALOXIFENE. Risk-benefit balance should be considered in patients taking RALOXIFENE. Risk-benefit balance should be considered in patients taking RALOXIFENE. Risk-benefit balance should be considered in patients taking RALOXIFENE.

PRECAUTIONS

General

Concurrent Estrogen Therapy—The concurrent use of RALOXIFENE and systemic estrogen therapy has not been studied in prospectively clinical trials and there are no controlled studies in such patients. RALOXIFENE and estrogen should not be used concomitantly.

Local Metabolism—RALOXIFENE is metabolized by liver enzymes. RALOXIFENE is metabolized by liver enzymes. RALOXIFENE is metabolized by liver enzymes. RALOXIFENE is metabolized by liver enzymes. RALOXIFENE is metabolized by liver enzymes.

Drug Interactions

Cholestyramine—Cholestyramine causes a 60% reduction in the absorption and hepatic uptake of RALOXIFENE and should not be coadministered with RALOXIFENE.

Warfarin—The coadministration of RALOXIFENE and warfarin has not been studied under clinical conditions. However, 10% decreases in prothrombin time have been observed in single-dose studies. If RALOXIFENE is given concurrently with warfarin, prothrombin time should be monitored.

Other Highly Protein-Bound Drugs—Raloxifene is more than 90% bound to plasma proteins. In vitro, raloxifene did not affect the binding of warfarin, phenytoin, or lamotrigine. Caution should be used when RALOXIFENE is coadministered with other highly protein-bound drugs, such as doxofylline, indomethacin, naproxen, ibuprofen, diazepam, and diazoxide.
Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis:
In a 21-month carcinogenicity study in mice, there was an increased incidence of ovarian tumors in female animals given 0 to 242 mg/kg, which included benign and malignant tumors of granulosa/theca cell origin and benign tumors of theca cell origin. Systemic exposure (AUC) of rafoxane in this group was 0.3 to 34 times that in postmenopausal women administered a 60-mg dose. There was also an increased incidence of testicular interstitial cell tumors and prostate adenomas and adenocarcinomas in mice given 41 to 210 mg/kg (6.8 to 24 times the AUC in humans) and prostatic hyperplasia in males given 210 mg/kg.

In a 2-year carcinogenicity study in rats, an increased incidence in ovarian tumors of granulosa/theca cell origin was observed in females given 279 mg/kg (approximately 400 times the AUC in humans). The female rodents in these studies were treated during their reproductive lives when their ovaries were functional and responsive to hormonal stimulation. The clinical relevance of these tumor findings is not known.

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

Impairment of Fertility:
When male and female rats were given daily doses of 25 mg/kg (0.8 times the human dose based on surface area, mg/m²) prior to and during mating, no pregnancies occurred. In male rats, daily doses up to 100 mg/kg (6.7 times the human dose based on surface area, mg/m²) for at least 2 weeks did not affect sperm production or quality or reproductive performance. In female rats, at doses of 0.1 to 10 mg/kg/day (0.02 to 1.6 times the human dose based on surface area, mg/m²), rafoxane disrupted estrus cycles and inhibited ovulation. These effects of rafoxane were reversible. In another study in rats in which rafoxane was given during the preimplantation period at doses of 0.1 mg/kg (0.02 times the human dose based on surface area, mg/m²), rafoxane delayed and disrupted embryo implantation, resulting in prolonged gestation and reduced litter size. The reproductive and developmental effects observed in animals are consistent with the estrogen receptor activity of rafoxane.

Pregnancy
Pregnancy Category X—EVISTA should not be used in women who are or may become pregnant (see CONTRAINDICATIONS).

Nursing Mothers—EVISTA should not be used by lactating women (see CONTRAINDICATIONS). It is not known whether rafoxane is excreted in human milk.

Pediatric Use—EVISTA should not be used in pediatric patients.

ADVERSE REACTIONS
The safety of rafoxane has been assessed primarily in 12 Phase 2 and Phase 3 studies with placebo, estrogen, and estrogen-progestin replacement therapy (HRT) control groups. The duration of treatment ranged from 2 to 30 months and 2036 women were exposed to rafoxane (371 patients received 10 to 50 mg/day, 828 received 60 mg/day, and 837 received 120 to 600 mg/day). The majority of adverse events occurring during clinical trials were mild and generally did not require discontinuation of therapy.

Therapy was discontinued due to an adverse event in 11.4% of 581 EVISTA-treated women and 12.2% of 584 placebo-treated women. Common adverse events consisted to be drug-related were hot flashes and leg cramps (see Table 4). The first occurrence of hot flashes was most commonly reported during the first 6 months of treatment. Discontinuation rates due to hot flashes did not differ significantly between EVISTA and placebo groups (1.7% and 2.2%, respectively).

Adverse Events in Placebo-controlled Clinical Trials:
Table 4 lists adverse events occurring in the placebo-controlled clinical trials at a frequency ≥2.0% in either group and in more EVISTA-treated women than in placebo-treated women. Adverse events are shown without attribution of causality.

Table 4. Adverse events occurring in placebo-controlled clinical trials at a frequency ≥2.0% and in more EVISTA-treated (60 mg once daily) women than placebo-treated women

<table>
<thead>
<tr>
<th>Body System</th>
<th>EVISTA 60 mg/Day %</th>
<th>Placebo 60 mg/Day %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection</td>
<td>15.1</td>
<td>14.8</td>
</tr>
<tr>
<td>Fio Synthesis</td>
<td>3.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Leg Cramps</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>3.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Pupil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flashes</td>
<td>24.6</td>
<td>18.3</td>
</tr>
<tr>
<td>Migraine</td>
<td>2.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Vomitting</td>
<td>3.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td>3.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Metabolic and Nutritional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Gain</td>
<td>8.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>3.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>10.7</td>
<td>10.1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>4.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Nervous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>6.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>10.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>5.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>2.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Sweating</td>
<td>3.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginitis</td>
<td>4.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Cystitis</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Endocrine Disorder</td>
<td>3.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* Treatment-emergent adverse related adverse event, including only patients with an intact uterus. EVISTA, EVISTA. Placebo, Placebo.

Comparison of EVISTA and Hormone Replacement Therapy Adverse Events

EVISTA was compared with estrogen-progestin replacement therapy (HRT) in 3 clinical trials. Table 5 shows adverse events occurring more frequently in the treatment group and at an incidence ≥2.0% in any group. Adverse events are shown without attribution of causality.
Table 5. Adverse events reported in clinical trials with EVISTA (60 mg once daily) and continuous combined or cyclic estrogen plus progestin (HRT) at an incidence >2.0% in any treatment group.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>EVISTA (N=621)</th>
<th>HRT-Continuous (N=996)</th>
<th>HRT-Cyclic (N=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urogenital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Pain</td>
<td>4.4</td>
<td>37.5</td>
<td>29.7</td>
</tr>
<tr>
<td>Vaginal Bleeding</td>
<td>6.6</td>
<td>64.2</td>
<td>88.5</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>1.6</td>
<td>12.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flashes</td>
<td>26.7</td>
<td>3.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>11.0</td>
<td>0</td>
<td>6.8</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>6.6</td>
<td>10.4</td>
<td>16.7</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2.8</td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1 Treatment-emergent adverse events included all events, not only those that were new. EVISTA, 60 mg; HRT-Continuous, 1.25 mg/0.625 mg; HRT-Cyclic, 1.25 mg/0.625 mg, 3.0 mg/1.25 mg, or 2.5 mg/1.5 mg, respectively. Logrank test for overall 1.25 mg/0.625 mg methisterone acetate vs 5 mg/5 mg estradiol valerate at 0.05 mg compared on Day 1 through 16 or 17 through 26.

Laboratory Changes

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

There were small decreases in serum total calcium, inorganic phosphate, total protein, and albumin which were generally of lesser magnitude than decreases observed during ERT/HRT. Platelet count was also decreased slightly and was not different from ERT.

Additional Safety Information

Incidence of estrogen-dependent cancers of the endometrium and breast are being evaluated across all completed and ongoing clinical trials involving 12,800 patients, of which approximately 8000 women have received at least one dose of raloxifene. The duration of exposure has been up to 39 months.

Endometrium—Compared to placebo, raloxifene did not increase the risk of endometrial cancer.

Breast—Compared to placebo, raloxifene did not increase the risk of breast cancer (see CLINICAL PHARMACOLOGY. Effects on the Breast).

OVERDOSAGE

Incidents of overdose in humans have not been reported. In an 8-week study of 63 postmenopausal women, a dose of raloxifene HCI 800 mg/day was safely tolerated. 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/m² or in monkeys at 1000 mg/kg (90 times the AUC in humans). There is no specific antidote for raloxifene.

DOSEAGE AND ADMINISTRATION

The recommended dosage is one 60 mg EVISTA tablet daily which may be administered any time of day without regard to meals. The effect of EVISTA on BMD beyond two years of treatment is not known at this time, but is being evaluated in ongoing clinical trials.

NOW SUPPLIED

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

<table>
<thead>
<tr>
<th>Bottle (count)</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 (unit of use)</td>
<td>0002-4165-30</td>
</tr>
<tr>
<td>100 (unit of use)</td>
<td>0002-4165-02</td>
</tr>
<tr>
<td>2000</td>
<td>0002-4165-07</td>
</tr>
</tbody>
</table>

Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP). The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F), that results in a mean kinetic temperature calculated to be not more than 25°C, and that allows for excursions between 10° and 30°C (50° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

CAUTION—Federal (USA) law prohibits dispensing without prescription.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815, S02

MEDICAL REVIEW(S)
Medical Team Leader Review of Labeling Supplement

NDA #20-815
Drug: Evista® (raloxifene hydrochloride)
Sponsor: Lilly Research Laboratories

Submission Date: July 24, 1998
Response to FDA Request: August 28, 1998

Background:

In December 1997, DODP was asked to review the same materials utilized by Lilly’s independent Oncology Advisory Board to adjudicate the breast cancer cases reported from clinical studies involving raloxifene. Clinical information, including case summaries and template versions of mammogram reports, pathology reports and operative reports, on a total of 42 patients was submitted. The Oncology Advisory Board was blinded to the treatment assignment of these cases, whereas DODP was not.

DODP concluded on 3/2/98 that 16 cases of invasive breast cancer had occurred on study, six on raloxifene and 10 on placebo. Cases of DCIS, cases that were determined to be pre-existing, or for which insufficient information was provided were excluded. DODP stated that “it will not be possible to retrospectively obtain sufficient information to justify a claim related to breast cancer prevention. The best strategy would be to mount a definitive breast cancer chemoprevention trial.” DODP did indicate however, that the following statements could be included in the Clinical Pharmacology section, Effects on the Breast subsection of product labeling:

Sponsor’s Labeling Proposal:

In a labeling supplement submitted 7/24/98, Lilly proposes the following as a new second paragraph in the Effects on the Breast subsection of the Clinical Pharmacology section:
In the Adverse Reactions section, Additional Safety Information subsection, the statement, "[blank]", will be added to the sentence: "Breast—Compared to placebo, raloxifene did not increase the risk of breast cancer."

FDA Response:
Each statement proposed by the sponsor is followed by comments and an FDA counter-proposal:

1. 
   
2. 
   
   The genesis of the comment by FDA that, "ascertainment of breast cancer cases was not systematically performed across all trials" stems from the fact that only 16 out of 42 breast cancers initially reported by Lilly ultimately had definitive documentation of invasive breast cancer that developed on study. Lilly contends that FDA’s statement is misleading and proposes this alternative, in view of the completeness of protocol-specified mammographic screenings. Note that each of the 16 definitive breast cancer cases occurred while the patient was on study. While Lilly admits that patients who discontinued early for reasons other than breast cancer were not routinely followed for additional adverse events, this does not appear to be relevant to the 16 cases being reported.
Recommended Regulatory Action:

Approval is recommended for the labeling supplement submitted 7/24/98 to NDA #20-815 for Evista® (raloxifene hydrochloride) with the following labeling revisions:

A new second paragraph in the Effects on the Breast subsection of the Clinical Pharmacology section:
cc:
HFD-510/ NDA #20-815
HFD-510/ E. Colman
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ S. Honig
HFD-150/ D. Pease

/S/ 9/4/95
Julie Beitz, MD Date

10/4/98

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL
Medical Officer Consult

Review: NDA 20-815, EVISTA™ (Raloxifene Hydrochloride)

HFD-510 Contact: Eric Colman, M.D.

Submission Received (HFD-150): July 29, 1997
Reviewing Medical Officer: Karen Johnson, M.D.
Review completed: August 6, 1997

Background: An NDA for raloxifene submitted to HFD-510 by Eli Lilly on June 8, 1997, was filed and given a priority review status. Raloxifene is a selective estrogen receptor modulator (SERM) that Lilly plans to market with an indication for osteoporosis prevention. Based on in vitro, preclinical, and limited clinical trial data, the sponsor also claims that this drug reduces the risk for breast cancer. HFD-510 has requested an opinion as to whether the methodology employed in the phase 3 osteoporosis trials was rigorous enough to support a claim that raloxifene reduces the risk for breast cancer. Information provided by HFD-150 with this consult request included one page from the NDA that provides the proposed text for the portion of the raloxifene label entitled "Effects on the Breast" (which claims a statistically significant reduction in breast cancer incidence with raloxifene treatment). Also provided were nine pages from a section (6.3. Breast) of the sponsor’s Integrated Summary of Safety.

Reviewer Comments: The data provided appear to be grossly insufficient to support a claim that raloxifene reduces breast cancer risk. Despite the summary nature of the information provided, it is unlikely that more information will improve the acceptability of the methodology or the credibility of the data used by the sponsor to conclude that raloxifene reduces the risk for breast cancer. It is stated in Section 6.3.2 that the analysis of raloxifene’s impact on breast cancer risk is based on 28 cases of breast cancer. The sponsor indicates that 13 cases were “pre-existing” at the time of study entry. We know of no rationale to support treatment of “pre-existing” breast cancer with raloxifene or placebo for a period of months or years until the breast cancer comes to subsequent clinical attention. Given the fundamental difference in the population of individuals with “pre-existing” breast cancer compared to individuals who would enter a study with no clinical or radiographic evidence of breast cancer, only the 15 non-pre-existing cases could be considered in evaluating the effects of raloxifene on the subsequent development of breast cancer.

Experience based on as few as 15 cases is inadequate to justify a claim of breast cancer risk or incidence reduction, because it is unlikely that this number of events is sufficient for the reliable detection of a difference between treatment groups. According to Dr. Colman, not all of the raloxifene studies included in the meta-analysis were designed to have a baseline mammogram at entry. Studies lacking a baseline mammogram should be considered inadequate to contribute to an analysis of breast cancer prevention. Excluding such studies would reduce the sample size and probably the number of cases in the analysis. As a point of reference, it should be noted that the NSABP Breast Cancer Prevention Trial with tamoxifen was designed with the anticipation that there would be at least 180 breast cancer events in only the 8,000 person placebo-control arm.

There are many other questions that could not be answered by review of the summary information provided in the consult package. The answers to these questions would bring to light additional information that could further weigh against the sponsor’s claim that raloxifene reduces breast cancer risk. The following questions are examples of the kind of review questions that would need to be answered to fully address the claim that raloxifene prevents breast cancer:

1. **OBJECTIVES/ENDPOINTS FOR BREAST CANCER PREVENTION PROTOCOLS.** The demonstration of breast cancer prevention should be documented prospectively, in a trial or trials specifically designed for this purpose. Study protocols should specify that patients/subjects will be monitored for the development of breast cancer and that breast cancer incidence is a primary endpoint. Without these measures, the studies could be flawed by a detection bias. For the raloxifene studies,
what procedures, in place from the beginning of each trial, were designed to monitor patient status with respect to the breast cancer endpoint? Was a baseline mammogram and clinical breast exam with no evidence of breast malignancy required before a participant could enter the raloxifene trials? Was an annual mammogram scheduled as part of the follow-up? Were follow-up breast physical exams part of the protocol and if so how frequently were they performed? What was the level of compliance with these protocol procedures?

2. **ADDITIONAL QUESTIONS RELATED TO DETECTION BIAS.** Evidence should be provided that differential ascertainment of cases or other factors did not cause bias. Was there a difference between the raloxifene vs. the control arms in the kind of breast cancer cases being detected? The stages and the histologies of all the breast cancer cases that were diagnosed in the course of the studies would have to be reviewed and compared according to study arm.

3. **ADEQUACY OF THE RANDOMIZATION.** Data should be provided that confirms the adequacy of the randomization. When the patient population receiving raloxifene is compared with the placebo population, the two groups at baseline should have been similar with respect to breast cancer risk factors. As part of the clinical data collection, were the variables needed to perform an estimate of breast cancer risk collected? (for the Gail model - number of breast biopsies, age of menarche, age at first live birth, number up to 2 of first degree relatives with a breast cancer history, etc.)

4. **PLAUSIBILITY OF RESULTS.** If the patient population participating in the osteoporosis trials are not representative of the general population, information should be provided that adequately describes the study population. Are the rates of breast cancer incidence in the placebo population consistent with the rate that would have been expected or predicted on the basis of the known characteristics of the group and the female population from which they were drawn?

**Recommendations:**

1. Although it is understood that the sponsor is not seeking a formal indication that raloxifene reduces breast cancer risk, the acceptance of such a claim anywhere in the label is, in reality, equivalent to granting approval for marketing raloxifene for the indication of breast cancer prevention. Normally, breast cancer prevention claims are reviewed by the Division of Oncology Drug Products (DODP) and discussed before the Oncologic Drugs Advisory Committee. Consequently, HFD-150 recommends that the sponsor request a meeting with DODP to facilitate the future development of raloxifene for the breast cancer prevention indication.

2. In conveying this information to the sponsor, the following language is suggested:
   In reviewing the proposed label for raloxifene as an agent that is indicated for the prevention of osteoporosis, it is not acceptable to include language elsewhere in the label that “there was a statistically significant reduction in the frequency of newly diagnosed breast cancer in raloxifene-treated women compared with placebo”. Acceptance of this claim would effectively provide the sponsor with a second indication for raloxifene without review by the Division of Oncology Drug Products or the Oncologic Drugs Advisory Committee. Consequently, it is recommended that the sponsor request a meeting with the Division of Oncology Drug Products to discuss the breast cancer prevention claim and the data that support it.

3. Information from the conclusions and points 1 to 4 should also be conveyed to the sponsor.

\[ /S/ \]
Karen Johnson, M.D., Ph.D.
3/6/97

\[ /S/ \]
Jürgen Beitz, M.D.
3/6/97
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815, S02

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS
March 15, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

FINAL PRINTED LABELING
for approved supplemental
NDA 20-815/S-002

RE: NDA 20-815—EVISTA® (raloxifene hydrochloride)

Reference is made to your letter of November 24, 1999. In that letter, the Lilly supplemental New Drug Application (July 24, 1999, S-002), was approved. That supplemental NDA provided for a revision in the Effects on the Breast subsection of the CLINICAL PHARMACOLOGY section, and in the Additional Information subsection of the ADVERSE REACTIONS section of the Evista package insert,

We are herewith submitting twenty (20) copies of the final printed labeling (FPL), ten of which have been mounted on heavy weight paper.

Please call Dr. Paul D. Gesellchen at (317) 276-4306 or me at (317) 276-4038 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas, Ph.D.
Director
U. S. Regulatory Affairs

Enclosures (PV 3081 AMP)
CSO REVIEW OF FPL

NDA 20-815
Evista (raloxifene hydrochloride) Tablets

FPL submission date: N/A
Date of approval for supplements: N/A
Date approved draft was submitted: November 19, 1998 + FAX'd
Labeling pieces reviewed: Approved FPL submitted December 19, 1997

Review and comments:

The approved Final Printed Labeling (FPL) submitted on December 19, 1997 is exactly the same as the draft labeling submitted on November 19, 1998 as supplement 002 with the following changes:

In the Effects on the Breast subsection of the CLINICAL PHARMACOLOGY section the following second paragraph is added:

The following partial sentence is inserted in the Additional Safety Information subsection of the ADVERSE REACTIONS section following the sentence, “Breast—Compared to pacebo, raloxifene did not increase the risk of breast cancer.”

The draft labeling submitted on November 19, 1998 is acceptable.

/ S /
Mr. Randy Hedin, PM

cc: NDA Arch
    HFD-510
    HFD-510/RHedin/11.24.98/N18938FL_RV2
Exclusivity Checklist

NDA: 20-815
Trade Name: **Evista Tablets**
Generic Name: **Raloxifene Hydrochloride**
Applicant Name: **ELI LILLY & CO.**
Division: **DMEDP, HFD-510**
Project Manager: **RANDY HEDIN**
Approval Date: **11-24-98**

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a. Is it an original NDA?  
      | Yes | No | ✓ |

   b. Is it an effectiveness supplement?  
      | Yes | ✓ | No |

   c. If yes, what type? (SE1, SE2, etc.)  
      | SEG |

      Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")  
      | Yes | ✓ | No |

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      Explanation: This supplement elaborates on the differences in incidence of breast cancer between Evista-treated and placebo patients; i.e., fewer cancers occurred in the Evista-treated group.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      Explanation:

   d. Did the applicant request exclusivity?  
      | Yes | No | ✓ |

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?  
   | Yes | ✓ | No |

   If yes, NDA # **20-815**

   Drug Name: **Evista**

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.**

3. Is this drug product or indication a DESI upgrade?  
   | Yes | No |

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE**
SIGNATURE BLOCKS (even if a study was required for the upgrade).

### PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

<table>
<thead>
<tr>
<th>1. Single active ingredient product.</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer &quot;yes&quot; if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer &quot;no&quot; if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

| Drug Product | |
| NDA # | |
| Drug Product | |
| NDA # | |
| Drug Product | |
| NDA # | |

<table>
<thead>
<tr>
<th>2. Combination product.</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer &quot;yes.&quot; (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

| Drug Product | |
| NDA # | |
| Drug Product | |
| NDA # | |
| Drug Product | |
| NDA # | |

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

### PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of
new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? Yes No

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

   Basis for conclusion:

   b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? Yes No

       1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

       If yes, explain:

       2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? Yes No

       If yes, explain:
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

<table>
<thead>
<tr>
<th>Investigation #1, Study #:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2, Study #:</td>
<td></td>
</tr>
<tr>
<td>Investigation #3, Study #:</td>
<td></td>
</tr>
</tbody>
</table>

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Investigation #3</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

<table>
<thead>
<tr>
<th>Investigation #1 -- NDA Number</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2 -- NDA Number</td>
<td></td>
</tr>
<tr>
<td>Investigation #3 -- NDA Number</td>
<td></td>
</tr>
</tbody>
</table>

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Investigation #3</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

<table>
<thead>
<tr>
<th>Investigation #1 -- NDA Number</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2 -- NDA Number</td>
<td></td>
</tr>
<tr>
<td>Investigation #3 -- NDA Number</td>
<td></td>
</tr>
</tbody>
</table>

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new");

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td></td>
</tr>
<tr>
<td>Investigation #3</td>
<td></td>
</tr>
</tbody>
</table>

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial
support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation #2</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation #3</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation #2</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation #3</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) If yes, explain:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
exclusivity checklist Section 3 G

Signature of PM/CSO
Date: 7/30/99

Signature of Division Director /S/
Date: 7/30/99

cc: Original NDA 20-8/5
Division File
HFD-93 Mary Ann Holovac

Appears this way on original

Appears this way on original

Back to top
PEDIATRIC PAGE
(Complete for all original application and all efficacy supplements)

<table>
<thead>
<tr>
<th>NDA/BLA Number:</th>
<th>20815</th>
<th>Trade Name:</th>
<th>EVISTA (RALOXIFENE HCL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplement Number:</td>
<td>2</td>
<td>Generic Name:</td>
<td>RALOXIFENE HCL</td>
</tr>
<tr>
<td>Supplement Type:</td>
<td>SE8</td>
<td>Dosage Form:</td>
<td>TAB</td>
</tr>
</tbody>
</table>
| Regulatory Action: | AP | Proposed Indication: | CLIN.PHARM.: changes "effects on the breast" section;
ADVERSE REACTIONS: changes "Additional Safety Information" section NO Pediatric Information |

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION? NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____ NeoNates (0-30 Days) ____ Children (25 Months-12 years)

____ Infants (1-24 Months) ____ Adolescents (13-16 Years)

Label Adequacy | Does Not Apply
Formulation Status | -
Studies Needed | -
Study Status | -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
This drug specifically states it is not to be used in children in the PRECAUTIONS section.

There is no need for studies in children. The drug is indicated for prevention of postmenopausal osteoporosis. A waiver has not yet been requested or granted, but this product is eligible for one.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ENID GALLIERS

Signature [Signature]

Date 7/27/99

DEBARMENT
CERTIFICATION

NDA Application No.: 20-815

Drug Name: EVISTA®, raloxifene hydrochloride

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory C. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: [Signature]

Gregory G. Enas, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: March 15, 1999
CERTIFICATION

NDA Application No.: NDA 20-815

Drug Name: EVISTA

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory C. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: [Signature]

Gregory C. Enas, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: July 24, 1998
November 19, 1998

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine  
Drug Products, HFD-510  
Attn: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857-1706

Re: NDA 20-815--EVISTA® (raloxifene hydrochloride) [S-002]

Reference is made to the submission (July 24, 1998) of a supplemental NDA (S-002) consisting of proposed changes to the Evista physician package insert. Reference is also made to a Fax communication (November 2, 1998) from Mr. Randy Hedin (FDA) to Dr. Paul Gesellchen (Lilly). This Fax contained FDA suggestions for revisions to the wording proposed by Lilly in the supplemental NDA.

Please also refer to Fax and phone communications between Dr. Gesellchen and Dr. Eric Colman (FDA) on November 9, 1998 and November 12, 1998. The conclusion from these communications was that the FDA would allow Lilly to include the breast cancer incidence rates per 1000 person-years (as parenthetical comments) and Lilly would accept all of the FDA proposed revisions contained in the Fax of November 2, 1998.

We are herewith providing a copy of the draft label changes. The changes to the existing physician package insert are denoted by large (18 point) font. The only additions to the November 2, 1998 Fax are the additions of the parenthetical phrase "(0.41 per 1000)" at the end of the third sentence and the addition of the parenthetical phrase "(1.43 per 1000)" at the end of the fourth sentence.
Please call Dr. Paul D. Gesellchen at (317) 276-4306 or me at (317) 276-4038 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

[Signature]

Gregory G. Enas, Ph.D.
Director
U. S. Regulatory Affairs

Enclosures

cc: Mr. Randy Hedin (desk copy by Fax)
August 28, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-815—EVISTA® (raloxifene hydrochloride)

Reference is made to the submission (July 24, 1998) of a supplemental NDA (S-002) consisting of proposed changes to the physician package insert. Reference is also made to a Fax communication (August 18, 1998) from Ms. Dotti Pease (FDA) to Dr. Paul Gesellchen (Lilly). This Fax contained four questions concerning the labeling supplement.

We are herewith providing written responses to the four questions (Attachment).

Please call Dr. Paul D. Gesellchen at (317) 276-4306 or me at (317) 276-4038 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas, Ph.D.
Director
U. S. Regulatory Affairs

Enclosures

cc: Ms. Dotti Pease (3 desk copies)
July 24, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-815--EVISTA® (raloxifene hydrochloride)

Reference is made to the submission to IND raloxifene hydrochloride (November 26, 1998, Serial No. 357) by Eli Lilly and Company (Lilly) of documents that were utilized by Lilly’s independent Oncology Advisory Board to adjudicate the breast cancer cases reported from clinical studies involving raloxifene. Reference is also made to the Fax communication (March 23, 1998) from Mr. Randy Hedin (FDA) to Dr. Paul Gesellchen (Lilly) regarding the November 26 submission (attachment). This Fax contained proposed wording regarding breast cancer that could be added to the product labeling for Evista.

Under 21 CFR §314.70(b) we are herewith submitting a supplemental New Drug Application (sNDA) to the referenced NDA. The full User Fee due for this sNDA has been submitted simultaneously with this submission (Form 3397 is provided). This sNDA recommends changes in the Effects on the Breast subsection of the CLINICAL PHARMACOLOGY section, and in the Additional Information subsection of the ADVERSE REACTIONS section of the Evista package insert.

The enclosed submission differs somewhat from the FDA recommended paragraph in several areas. The location and rationale for those differences are as follows:

The FDA recommended that the first sentence state:

Ascertainment of breast cancer cases was not systematically performed across all trials.

Lilly believes that this statement is misleading in that we did require annual or biannual mammograms from all patients in all placebo-controlled trials that were at least one year in duration. Many of our clinical trials are global in scope and in some European countries annual mammograms are in conflict with the local standard of care; therefore, biannual mammograms were performed in those locations. During all of our clinical investigations with raloxifene, breast cancer cases were reported as serious adverse events and
systematically recorded with appropriate follow-up. In addition, for each reported case of breast cancer, Lilly requested mammograms, pathology slides, and additional information to facilitate an independent review by the Oncology Advisory Board. The proposed wording by Lilly does however acknowledge that ascertainment of cases occurring after early trial discontinuation was not systematic. By this it is meant that events which occurred in subjects after early discontinuation were not solicited, but they were recorded if reported to Lilly by the patient or her physician. Thus, the revised section will read:

In the original FDA proposed wording the next two sentences described the incidence of newly diagnosed breast cancer. That proposal read:

Filling in the appropriate numbers that section would read

Lilly recommends that for simplicity and clarification, the rate of exposure be expressed as events per 1000 person-years. Thus, the section will state:
In the final sentence the FDA proposed wording states:

Lilly believes that this statement appears to suggest the treatment of breast cancer rather than the prevention of breast cancer. This concept was discussed the FDA in a phone conversation between Ms. Dottie Pease (FDA) and Dr. Gesellchen (Lilly) on March 26, 1998. In that conversation, Ms. Pease agreed that the word “reducing” might be more appropriately replaced with the word “preventing”. To reflect the fact that the clinical trials where these observations have been made are proceeding into their fourth year with the possibility of further extension, the word “yet” has also been added. The final sentence now reads:

Finally, we have added the following reference sentence to the Additional Information subsection of the ADVERSE EVENTS section:

(See CLINICAL PHARMACOLOGY, Effects on the Breast)

We are enclosing three copies of the draft package insert labeling (identified as PV 3080-A AMP). Please note, when reviewing the package insert labeling, that the new wording is highlighted by enlarged, bold type and deletions to the document have been identified by strikethroughs.

Please call Dr. Paul D. Gesellchen at (317) 276-4306 or me at (317) 276-4038 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas, Ph.D.
Director
U. S. Regulatory Affairs

cc: Ms. Dottie Pease (three desk copies)

Enclosures