CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020815, S02

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative/ Correspondence Document(s)	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020815, S02

APPROVAL LETTER

NDA 20-815/S-002

NOV 24 1998

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

Dear Dr. Enas::

Please refer to your supplemental new drug application dated July 24, 1998, received July 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evista (raloxifene hydrochloride) Tablets.

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,

/S/ 11. 24. 98

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

/S/

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815, S02

PRINTED LABELING

PV 3081 AMP

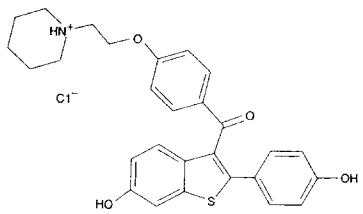
EVISTA®

Raloxifene Hydrochloride

60 mg Tablets

DESCRIPTION

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



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

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Decreases in estrogen levels after oophorectomy or menopause lead to increases in bone resorption and bone loss. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. 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 radiocalcium kinetics studies for decreased bone resorption and increases in bone mineral density (BMD).

Raloxifene's biological 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 uterine and breast tissues. Preliminary clinical data (through 30 months) suggest EVISTA lacks estrogen-like effects on uterus and breast tissue.

Pharmacokinetics

The disposition of raloxifene has been evaluated in 276 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 30% coefficient of variation) of most pharmacokinetic parameters. Table 1 summarizes the pharmacokinetic parameters of raloxifene.

Absorption

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

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

Distribution

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

Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins. Raloxifene binds to both albumin and α1-acid glycoprotein, but not to sex steroid binding globulin. In vitro, raloxifene did 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 ^{14}C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: raloxifene-4′-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4′-diglucuronide. No other metabolites have been detected, providing strong evidence that raloxifene is not metabolized by cytochrome P450 pathways. Unconjugated raloxifene comprises less than 1% of the total radiolabeled material in plasma. The terminal log-linear portions of the plasma concentration curves for raloxifene and the glucuronides are generally parallel. This is consistent with interconversion of raloxifene and the glucuronide metabolites.

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

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

Excretion

Raloxifene is primarily excreted in feces, and less than 0.2% is excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates. 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 raloxifene pharmacokinetic parameters in the healthy postmenopausal woman

	C_{max}[a] (ng/mL)/ (mg/kg)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$[a] (ng•hr/mL)/ (mg/kg)	CL/F (L/kg•hr)	V/F (L/kg)
Single Dose					
Mean	0.50	27.7	27.2	44.1	2348
CV (%)	52	10.7 to 273[b]	44	46	52
Multiple Dose					
Mean	1.36	32.5	24.2	47.4	2853
CV (%)	37	15.8 to 86.6[b]	36	41	56

Abbreviations: C_{max} = maximum plasma concentration, $t_{1/2}$ = half-life, AUC = area under the curve, CL = clearance, V = volume of distribution, F = bioavailability, CV= coefficient of variation.
[a] Data normalized for dose in mg and body weight in kg.
[b] Range of observed half-life.

Special Populations

Geriatric—No differences in raloxifene pharmacokinetics were detected with regard to age (range 42 to 84 years).

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

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

Race—Pharmacokinetic differences due to race have been studied on a limited basis in 1053 women consisting of 93.5% Caucasian, 4.3% Hispanic, 1.2% Asian, and 0.5% Black in the osteoporosis prevention trials. There were no discernible differences in raloxifene plasma concentrations among these groups; however, the influence of race cannot be effectively determined.

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

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

Drug-Drug Interactions

Clinically significant drug-drug interactions are discussed in PRECAUTIONS.

Ampicillin—Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with coadministration of ampicillin. These reductions are consistent with decreased-enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected. Therefore, EVISTA can be concurrently administered with ampicillin.

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

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

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

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

Animal Pharmacology

The skeletal effects of raloxifene treatment were assessed in ovariectomized rats and monkeys. In rats, raloxifene prevented increased bone resorption and bone loss after ovariectomy. There were positive effects of raloxifene on bone strength, but the effects varied with time. Cynomolgus monkeys were treated with raloxifene or conjugated estrogens for 2 years, equivalent at the bone level to approximately 6 years in humans. Raloxifene and estrogen increased BMD, but variability among animals obscured the ability to detect effects of either treatment on biomechanical strength. However, bone strength was positively correlated to BMD in both raloxifene- and estrogen-treated monkeys, indicating that BMD is a reasonable marker for bone strength.

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

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

Clinical Studies

Effects on Total Body and Regional Bone Mineral Density

In postmenopausal women, EVISTA preserves bone mass and increases BMD relative to calcium alone at 24 months. The effect on hip bone mass is similar to that for the spine. The relationships 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, 619 women who had undergone hysterectomy. In these trials, all women received calcium supplementation (400 to 600 mg/day). Women enrolled in these studies had a median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years postmenopause). The majority of the women were Caucasian (93.5%). Women were included if they had spine bone mineral density between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women. The mean T scores (number of standard deviations above or below the mean in healthy young women) for the 3 studies ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD. EVISTA, 60 mg administered once daily, produced increases in bone mass versus calcium supplementation alone, as reflected by dual-energy x-ray absorptiometric (DXA) measurements of hip, spine, and total body BMD. Compared with placebo, the increases in BMD for each of the 3 studies were statistically significant at 12 months and were maintained at 24 months (Table 2). The calcium-supplemented placebo groups lost approximately 1% of BMD over 24 months. (See figures below for total hip results.)

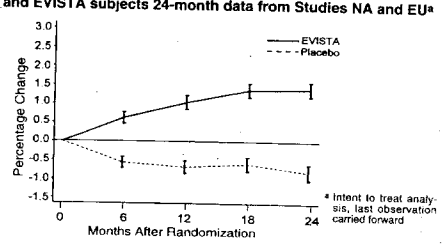
Table 2. EVISTA (60 mg once daily) related increases in BMD for the three osteoporosis prevention studies expressed as mean percentage increase versus calcium-supplemented placebo at 24 months[a]

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

Abbreviations: NA = North American, EU = European, INT = International.
[a] Intent-to-treat analysis; last observation carried forward.
[b] All women in the study had previously undergone hysterectomy.

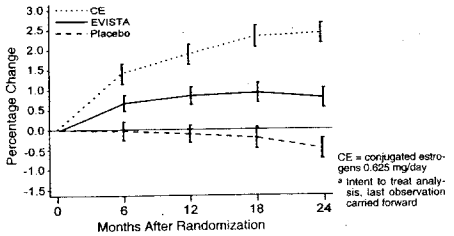
EVISTA also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's Triangle (hip) by 3.1% to 4.0%. The effects of EVISTA on forearm BMD were inconsistent between studies. In Study EU, EVISTA prevented bone loss at the ultradistal radius, whereas in Study NA, it did not.

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



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

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



Assessments of Bone Turnover

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

In the osteoporosis prevention trials, EVISTA therapy resulted in consistent, statistically significant suppression of bone resorption and bone formation, as reflected by changes in serum and urine markers of bone turnover (e.g., bone-specific alkaline phosphatase, osteocalcin, and collagen breakdown products). The suppression of bone turnover markers was evident by 3 months and persisted throughout the 24-month observation period.

Bone Histomorphometry

The tissue- and cellular-level effects of raloxifene were assessed by histomorphometric evaluation of human iliac crest bone biopsies taken after administration of a fluorochrome substance to label areas of mineralizing bone. The effects of EVISTA on bone histomorphometry were determined by pre- and post-treatment biopsies in a 6-month study of Caucasian postmenopausal women who received once-daily doses of EVISTA 60 mg or 0.625 mg conjugated estrogens. Ten raloxifene-treated and 8 estrogen-treated women had evaluable bone biopsies at baseline and after 6 months of therapy. Bone formation rate/bone volume and activation frequency, the primary efficacy parameters, decreased to a greater extent with conjugated estrogen treatment versus EVISTA treatment, although the differences were not statistically significant. Bone in EVISTA- and estrogen-treated women showed no evidence of mineralization defects, woven bone, or marrow fibrosis. In a blinded ongoing study, light microscopic evaluation of transiliac biopsies taken at baseline and after 2 years of therapy in 59 postmenopausal women receiving placebo, 60 mg-, or 120 mg-raloxifene hydrochloride showed no osteomalacia, osteocyte damage, woven bone, marrow fibrosis, or other abnormalities.

Effects on Lipid Metabolism

The effects of EVISTA on selected lipid fractions and clotting factors were evaluated in a 6-month study of 390 postmenopausal women. EVISTA was compared with oral continuous combined estrogen/progestin (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate, [HRT]) and placebo (Table 3). EVISTA decreased serum total and LDL cholesterol without effects on serum total HDL cholesterol or triglycerides. In addition, EVISTA significantly decreased serum fibrinogen and lipoprotein (a).

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

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

Abbreviations: HRT = continuous combined estrogen/progestin (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate).
[a] Significantly different from placebo ($p<0.05$).
[b] Significantly different from HRT ($p<0.05$).

In the osteoporosis prevention studies (N=1764), 24-month data were consistent with results from the 6-month study. Compared with placebo, EVISTA significantly decreased serum total and LDL cholesterol by approximately 5% and 8% respectively, but did not affect HDL cholesterol or triglycerides.

Effects on the Uterus

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. Endometrial thickness measurements in raloxifene-treated women were indistinguishable from placebo. There were no differences between the raloxifene and placebo groups with respect to the incidence of reported vaginal bleeding.

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

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

Effects on the Breast

Across all placebo-controlled trials, EVISTA was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. EVISTA was associated with significantly less breast pain and tenderness than reported by women receiving estrogens with or without added progestin (see ADVERSE REACTIONS and Table 5).

Mammograms were routinely performed on an annual or biannual basis in all placebo-controlled clinical trials lasting at least 12 months. Independent review has determined that 16 cases (raloxifene and placebo combined) represented newly-diagnosed invasive breast cancer. Among 7017 women randomized to raloxifene, there were 6 cases of invasive breast cancer per 14,605 person-years of follow-up (0.41 per 1000). Among 3368 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

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

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

Supplemental calcium should be added to the diet if daily intake is inadequate.

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

CONTRAINDICATIONS

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

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

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

WARNINGS

Venous Thromboembolic Events—An analysis of EVISTA-treated women across all placebo-controlled clinical trials showed an increased risk of venous thromboembolic events defined as deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. The greatest risk for thromboembolic events occurs during the first 4 months of treatment. EVISTA should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and EVISTA therapy should be resumed only after the patient is fully ambulatory. Patients should be advised to avoid prolonged restrictions of movement during travel. The risk-benefit balance should be considered in women at risk of thromboembolic disease for other reasons, such as congestive heart failure and active malignancy.

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 (see CONTRAINDICATIONS).

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

PRECAUTIONS

General

Concurrent Estrogen Therapy—The concurrent use of EVISTA and systemic estrogen or hormone replacement therapy (ERT or HRT) has not been studied in prospective clinical trials and therefore concomitant use of EVISTA with systemic estrogens is not recommended.

Lipid Metabolism—EVISTA lowers serum total and LDL cholesterol by 6% to 11%, but does not affect serum concentrations of total HDL cholesterol or triglycerides. These effects should be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidemia.

Concurrent use of EVISTA and lipid-lowering agents has not been studied.

Endometrium—EVISTA has not been associated with endometrial proliferation (see **Clinical Studies** and ADVERSE REACTIONS). Unexplained uterine bleeding should be investigated as clinically indicated.

Breast—EVISTA has not been associated with breast enlargement, breast pain, or an increased risk of breast cancer (see **Clinical Studies** and ADVERSE REACTIONS). Any unexplained breast abnormality occurring during EVISTA therapy should be investigated.

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

Use in Men—Safety and efficacy have not been evaluated in men.

Information for Patients

For safe and effective use of EVISTA, the physician should inform patients about the following:

Patient Immobilization—EVISTA should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and patients should be advised to avoid prolonged restrictions of movement during travel because of the increased risk of venous thromboembolic events.

Hot flashes or flushes—EVISTA is not effective in reducing hot flashes or flushes associated with estrogen deficiency. In some asymptomatic patients, hot flashes may occur upon beginning EVISTA therapy.

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

Physicians should instruct their patients to read the patient package insert before starting therapy with EVISTA and to re-read it each time the prescription is renewed.

Drug Interactions

Cholestyramine—Cholestyramine causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene and should not be coadministered with EVISTA.

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

Other Highly Protein-Bound Drugs—Raloxifene is more than 95% bound to plasma proteins. In vitro, raloxifene did not affect the binding of warfarin, phenytoin, or tamoxifen. Caution should be used when EVISTA is coadministered with other highly protein-bound drugs, such as clofibrate, 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 9 to 242 mg/kg, which included benign and malignant tumors of granulosa/theca cell origin and benign tumors of epithelial cell origin. Systemic exposure (AUC) of raloxifene 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 prostatic adenomas and adenocarcinomas in males given 41 or 210 mg/kg (4.7 or 24 times the AUC in humans), and prostatic leiomyoblastoma 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:

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

Impairment of Fertility:

When male and female rats were given daily doses ≥5 mg/kg (≥0.8 times the human dose based on surface area, mg/m^2) prior to and during mating, no pregnancies occurred. In male rats, daily doses up to 100 mg/kg (16 times the human dose based on surface area, mg/m^2) 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/m^2), raloxifene disrupted estrous cycles and inhibited ovulation. These effects of raloxifene were reversible. In another study in rats in which raloxifene was given during the preimplantation period at doses ≥0.1 mg/kg (≥0.02 times the human dose based on surface area, mg/m^2), raloxifene 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 raloxifene.

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 raloxifene is excreted in human milk.

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

ADVERSE REACTIONS

The safety of raloxifene 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 raloxifene (371 patients received 10 to 50 mg/day, 828 received 60 mg/day, and 837 received from 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 considered 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 trial database 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

Body System	EVISTA N=581 %	Placebo N=584 %
Body as a Whole		
Infection	15.1	14.6
Flu Syndrome	14.6	13.5
Leg Cramps	5.9	1.9
Chest Pain	4.0	3.6
Fever	3.1	2.6
Cardiovascular		
Hot Flashes	24.6	18.3
Migraine	2.4	2.1
Digestive		
Nausea	8.8	8.6
Dyspepsia	5.9	5.8
Vomiting	3.4	3.3
Flatulence	3.1	2.4
Gastrointestinal Disorder	3.3	2.1
Gastroenteritis	2.6	2.1
Metabolic and Nutritional		
Weight Gain	8.8	6.8
Peripheral Edema	3.3	1.9
Musculoskeletal		
Arthralgia	10.7	10.1
Myalgia	7.7	6.2
Arthritis	4.0	3.6
Nervous		
Depression	6.4	6.0
Insomnia	5.5	4.3
Respiratory		
Sinusitis	10.3	6.5
Pharyngitis	7.6	7.2
Cough Increased	6.0	5.7
Pneumonia	2.6	1.5
Laryngitis	2.2	1.4
Skin and Appendages		
Rash	5.5	3.8
Sweating	3.1	1.7
Urogenital		
Vaginitis	4.3	3.6
Urinary Tract Infection	4.0	3.9
Cystitis	3.3	3.1
Leukorrhea	3.3	1.7
Endometrial Disorder[a]	3.1	1.9

[a] Treatment-emergent uterine-related adverse event, including only patients with an intact uterus: EVISTA, n=354; Placebo, n=364.

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 one 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[a]

Adverse Event	EVISTA (N=317) %	HRT-Continuous Combined (N=96) %	HRT-Cyclic (N=219) %
Urogenital			
Breast Pain	4.4	37.5	29.7
Vaginal Bleeding[b]	6.2	64.2	88.5
Digestive			
Flatulence	1.6	12.5	6.4
Cardiovascular			
Hot flashes	28.7	3.1	5.9
Body as a Whole			
Infection	11.0	0	6.8
Abdominal Pain	6.6	10.4	18.7
Chest Pain	2.8	0	0.5

[a] These data are from both blinded and open-label studies.
[b] Treatment-emergent uterine-related adverse event, including only patients with an intact uterus: EVISTA, n=290, HRT-Continuous Combined, n=67, HRT-Cyclic, n=217.
Continuous Combined HRT = 0.625 mg conjugated estrogens plus 2.5-mg medroxyprogesterone acetate.
Cyclic HRT = 0.625 mg conjugated estrogens for 28 days with concomitant 5 mg medroxyprogesterone acetate or 0.15 mg norgestrel on days 1 through 14 or 17 through 28.

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

Incidences of estrogen-dependent carcinoma of the endometrium and breast are being evaluated across all completed and ongoing clinical trials involving 12,802 patients, of which approximately 8300 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 HCl 600 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/m^2) or in monkeys at 1000 mg/kg (80 times the AUC in humans). There is no specific antidote for raloxifene.

DOSAGE 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.

HOW SUPPLIED

EVISTA 60-mg tablets are white, elliptical, 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:

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

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 15° and 30°C (59° 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)

ORIGINAL

OCT 4 1998

Medical Team Leader Review of Labeling Supplement

NDA #20-815
Drug: Evista[R] (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:

[redacted]

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:

[redacted]

[redacted]

In the **Adverse Reactions** section, **Additional Safety Information** subsection, the statement, "[redacted], 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:

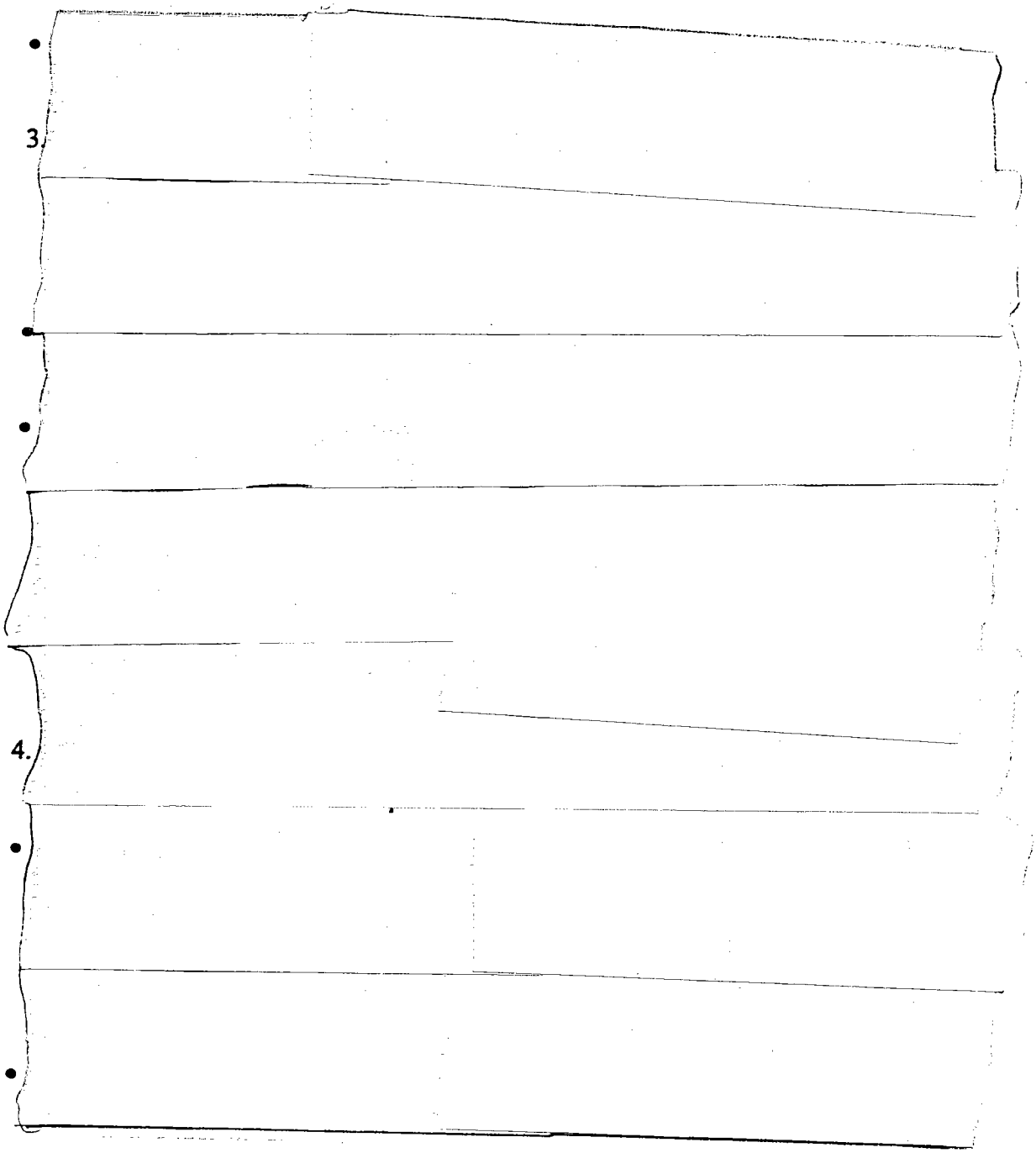
1. [redacted]

- [redacted]

- [redacted]

2. [redacted]

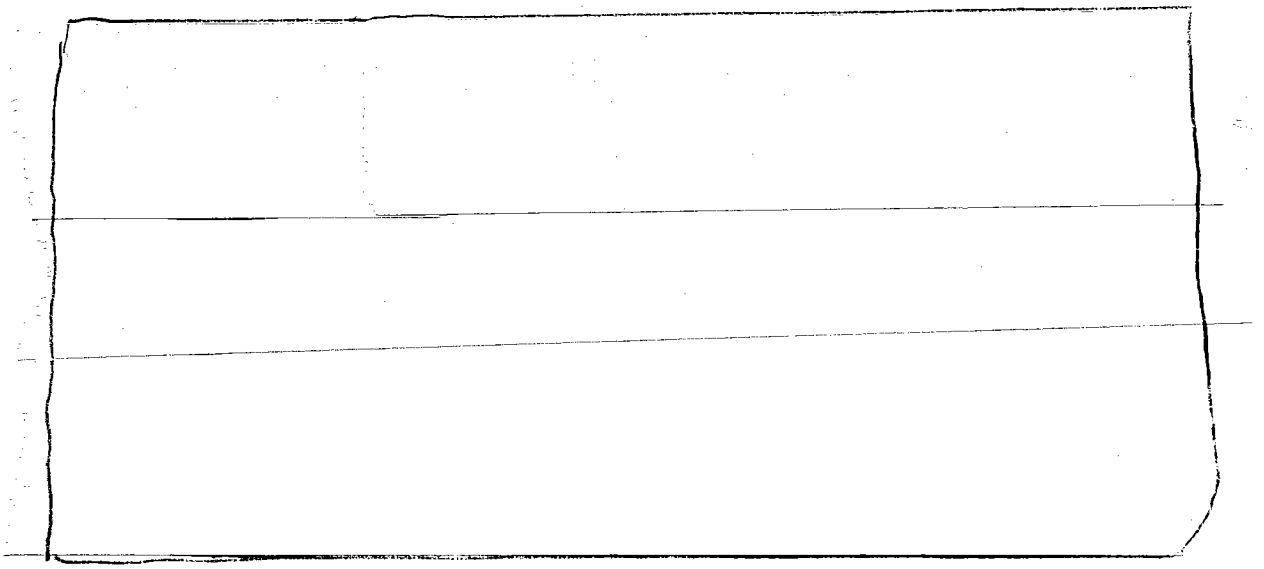
- The genesis of the comment by FDA that, "ascertainment of breast cancer cases was not systematically performed across all trials" stems from the fact that only 16 out of 42 breast cancers initially reported by Lilly ultimately had definitive documentation of invasive breast cancer that developed on 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[R] (raloxifene hydrochloride) with the following labeling revisions:

A new second paragraph in the **Effects on the Breast** subsection of the **Clinical Pharmacology** section:



/S/ 9/14/98
Julie Beitz, MD Date

APPEARS THIS WAY
ON ORIGINAL

/S/
10/4/98

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

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

AUG 6 1997

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*, preclinial, 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. <u>OBJECTIVES/ENDPOINTS FOR BREAST CANCER PREVENTION PROTOCOLS</u>. 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/ 8/6/97

Karen Johnson, M.D., Ph.D.

/S/ 8/6/97

Julie Beitz, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815, S02

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

SE8-002 FA

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

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

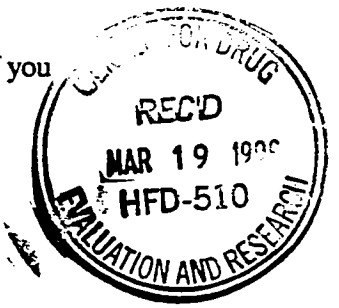
FINAL PRINTED LABELING
for approved supplemental
NDA 20-815/S-002

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. Geselchen 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

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

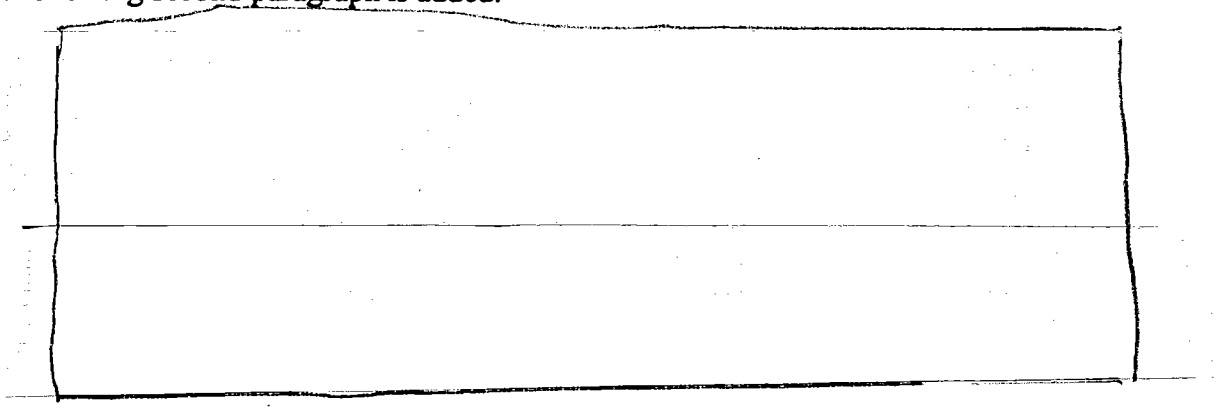
Date approved draft was submitted: November 19, 1998 + FAX'd

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 brest 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.)	SE8			
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)				
1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" 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 "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	
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 #				
2. Combination product.	Yes		No	
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 "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
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.	Yes		No	

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.	Yes		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:

Investigation #1, Study #:	
Investigation #2, Study #:	
Investigation #3, Study #:	

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.")

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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?

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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"):

Investigation #1	
Investigation #2	
Investigation #3	

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?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
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?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
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.)	Yes		No	
If yes, explain:				

BACK TO TOP

/S/

Signature of PM/CSO
Date: 7.30.99

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

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-815
HFD-510/Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20815	**Trade Name:**	EVISTA (RALOXIFENE HCL)
Supplement Number:	2	**Generic Name:**	RALOXIFENE HCL
Supplement Type:	SE8	**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	CLIN.PHARM.: changes "effects on the breast" section; ADVERSE REACTIONS: changes "Additonal 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	-

APPEARS THIS WAY ON ORIGINAL

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

/S/ 7/27/99

Signature Date

APPEARS THIS WAY ON ORIGINAL

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: Gregory D Enas
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: Gregory D Enas
Gregory C. Enas, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: July 24, 1998

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIGINAL
BL
DRUG AMENDMENT

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

NDA AMENDMENT

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.

Reviewers
Reviewed
Fax copy:
See Fax
dictated
Nov 19, 1998
/S/

REVIEWS COMPLETED
CSE[illegible]CTION:
[illegible] ☐ N.A.I. ☐ MEMO
/S/ 11/24/98
DATE
CSO INITIALS See Fax

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: Mr. Randy Hedin (desk copy by Fax)

SE8-002 BL

Lilly ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 28, 1998

NDA SUPPL AMENDMENT

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

NDA AMENDMENT

/S/
9-9-98

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.

/S/
9/1/98

Sincerely,

ELI LILLY AND COMPANY

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

Enclosures

cc: Ms. Dotti Pease (3 desk copies)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

/S/
9/10/98

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 27 1998
HFD-510

July 24, 1998

NDA NO. 20815 REF. NO. 002
NDA SUPPL FOR SE8-

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

SUPPLEMENT
Expedited Review Requested

/S/

/S/

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.

/S/ 8-31-98

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

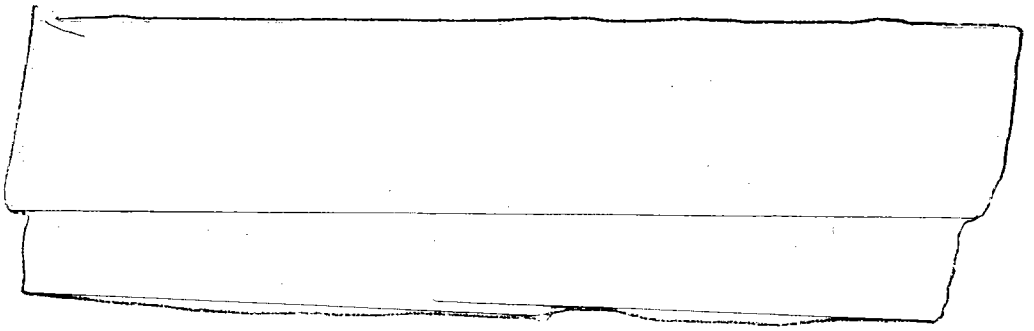
The FDA recommended that the first sentence state:

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

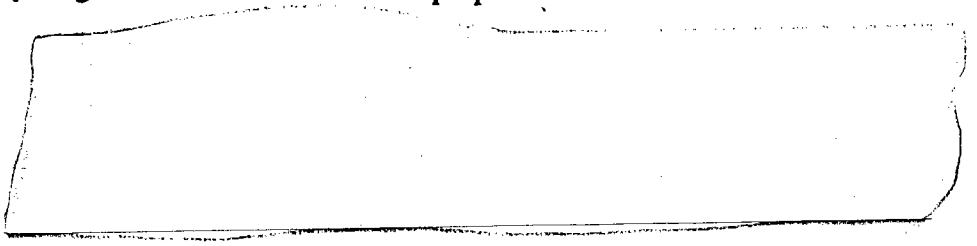
/S/ 9-1-98

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

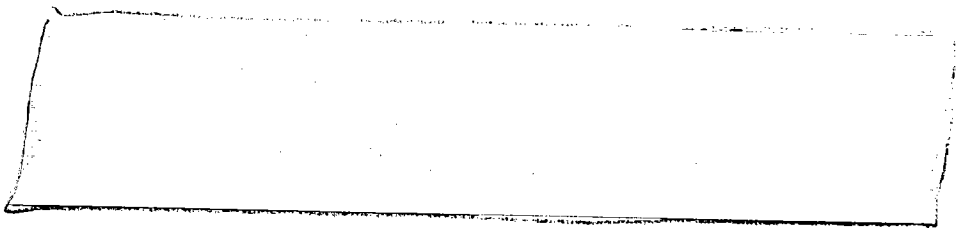
systematically recorded with appropriate follow-up. In addition, for each reported case of breast cancer, Lilly requested mammograms, pathology slides, and additional information to facilitate an independent review by the Oncology Advisory Board. The proposed wording by Lilly does however acknowledge 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:



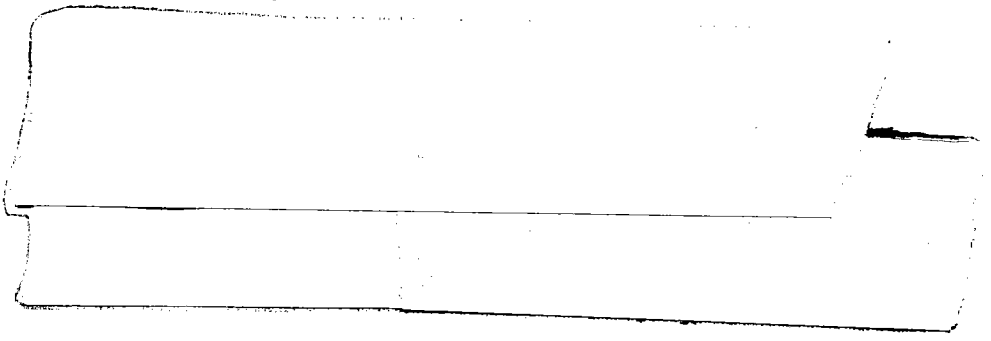
In the original FDA proposed wording the next two sentences described the incidence of newly diagnosed breast cancer. That proposal read:



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:

[redacted]

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:

[redacted]

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

(See CLINICAL PHARMACOLGY, 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

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

cc: Ms. Dottie Pease (three desk copies)

Enclosures

REVIEWS COMPLETED
CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO
11/24/98
DATE
CSO INITIALS