Table 18: Mean (CV) Pharmacokinetic Parameters of Raloxifene Following 120-mg dose of Raloxifene HCl

Parameter	Arithmetic Mean (CV) Males	Females (first dose)	Females (second dose)
Cmax (ng/mL)	0.595 (36.1%)	0.895 (29.2%)	0.859 (46.4%)
Dose/Wt. Normalized Cmax (ng/mL)/(mg/kg)	0.414 (36.2%)	0.605 (33.8%)	0.562 (38.2%)
Tmax (hr)	6.0[b]	6.0[b]	6.0[b]
AUC0-t (ng,hr/mL)	18.9 (59.2%)	27.4 (33.9%)	26.2 (51.8%)
AUC0-∞ (ng,hr/mL)	26.6 (49.0%)	34.6 (37.4%)	34.4 (53.4%)
Dose/Wt. Normalized AUC0-∞ (ng,hr/mL)/(mg/kg)	18.1 (42.9%)	23.3 (41.5%)	22.5 (50.2%)
t1/2 (hr)	26.4[c]	24.7[c]	20.9[c]
MRT (hr)	51.0 (43.7%)	46.0 (42.4%)	55.7 (108.2%)
Clp/F (L/hr/kg)	69.4 (52.4%)	49.0 (31.6%)	55.0 (40.5%)
Vss/F (L/kg)	2996 (29.4%)	2046 (27.1%)	2293 (53.0%)

[a] n=14
[b] median (range)
[c] harmonic mean (range)

Table 19: Mean (CV) Pharmacokinetic Parameters of Raloxifene-4'-Glucuronide and Raloxifene-6-Glucuronide Following 120-mg dose of Raloxifene HCl

Parameter	Arithmetic Mean (CV) [a] Males	Females (first dose)	Females (second dose)
	Raloxifene-4'-Glucuronide		
Cmax (ng-equiv/mL)	274.4 (63.0%)	277.1 (50.2%)	291.5 (65.1%)
Tmax (hr)	1.0[b] (0.5 to 6)	1.0[b] (0.5 to 4)	1.0[b] (0.5 to 6)
AUC0-t (ng-equiv, hr/mL)	4070.0 (54.6%)	3444.2 (49.4%)	3119.9 (41.4%)
AUC0-∞ (ng-equiv,hr/mL)	4441.9 (52.6%)	4834.1 (102.9%)	3498.8 (49.9%)
Dose/Wt. Normalized AUC0-∞ (ng-equiv,hr/mL)/(mg/kg)	2927.6 (34.8%)	3148.0 (96.4%)	2268.4 (44.2%)

$t_{1/2}$ (hr)	18.6[c]	17.5[c]	12.8[c]
	Raloxifene-6-Glucuronide		
C_{max} (ng-equiv/mL)	41.4 (57.7%)	41.1 (40.0%)	44.6 (56.9%)
T_{max} (hr)	6.0[b]	2.0[b]	2.0[b]
AUC_{0-t} (ng-equiv,hr/mL)	849.6 (61.0%)	834.6 (53.4%)	702.4 (46.6%)
$AUC_{0-\infty}$ (ng-equiv,hr/mL)	1111.3 (50.4%)	1429.0 (123.2%)	952.1[d] (50.9%)
Dose/Wt. Normalized $AUC_{0-\infty}$ (ng-equiv,hr/mL)/(mg/kg)	737.4 (33.4%)	932.7 (116.3%)	639.9[d] (49.5%)
$t_{1/2}$ (hr)	17.1[c]	17.3[c]	11.8[c,d]

a n=14 unless otherwise noted
b median (range)
c harmonic mean (range)
d n=13; subject 1864 excluded, terminal elimination phase could not be evaluated.

Table 20: Mean Raloxifene, Raloxifene-4'-Glucuronide, and Raloxifene-6-Glucuronide as a Percentage of TRHP AUC0-∞ Following 120-mg dose of Raloxifene HCl

	Arithmetic Mean of Percent[a]		
	Males	**Females (first dose)**	**Females (second dose)**
Raloxifene/TRHP	0.46%	0.73%	0.71%
Raloxifene-4'-glucuronide/TRHP	59.4%	66.9%	61.2%
Raloxifene-6-glucuronide/TRHP	13.4%	14.9%	14.2%[b]
Combined[c]	73.3%	82.5%	76.1%

a Raloxifene-4'-glucuronide and raloxifene-6-glucuronide AUC were first converted to raloxifene ng-equivalents.
b n=13; subject 1864 excluded, terminal elimination phase could not be evaluated.
c sum of raloxifene/TRHP, Raloxifene-4'-glucuronide/TRHP and Raloxifene-6-glucuronide/TRHP.

The within- and between-subject variability was investigated in females for raloxifene and its metabolites. Raloxifene with-in subject variability was approximately 30% and between-subject variability approximately 40%. For the metabolites, within-subject variability was approximately 23% and between subject variability was approximately 50%.

The following conclusions were drawn from this study.

1. The within-subject coefficient of variation estimates of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for raloxifene were 28.4% to 32.3%. The between-subject coefficient of variation for raloxifene was approximately 30% to 40%.

2. Gender differences were observed in some, but not all, pharmacokinetic parameters for raloxifene. Female subjects achieved higher C_{max} values, larger AUC_{0-t}, and smaller volumes of distribution (V_{ss}/F) than did

male subjects ($p<0.05$). These differences were not as significant when pharmacokinetic parameters were adjusted for lean body weight.

3. Pharmacokinetic parameters for raloxifene metabolites (raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and TRHP) were not significantly different between male and female subjects.

4. The terminal log-linear portion of plasma concentrations curve for raloxifene and metabolites are relatively parallel. This parallel decline in terminal phase, along with the relative stability of the ratios of raloxifene- and metabolites-to-TRHP 12 or more hours after the dose, is suggestive of interconversion between raloxifene and glucuronide metabolites.

5. The pharmacokinetic data collected in males was similar to that achieved in females. Under the current proposed indication males will not receive this drug.

VI. Drug Interactions

In vitro

In vitro studies were carried out to assess the protein binding characteristics of raloxifene. The drug is highly bound to plasma proteins; albumin but somewhat less to α-1-acid glycoprotein No specific gender or erythrocyte/plasma partition information was provided. There was no difference between the percent of raloxifene bound to proteins in plasma from healthy subjects and postmenopausal females. The binding appeared to be consistent over the raloxifene concentration . The presence of the glucuronide conjugates did not alter the percent bound from that without the conjugates.

Additional studies were conducted to evaluate raloxifene's ability to alter the binding capacity of other highly bound or narrow therapeutic index drugs. The ability of raloxifene to bind to sex hormone binding globulins (SHBG, also referred to as SBP--sex steroid binding protein) was also evaluated in response to a specific question addressed by the Agency. The question was, "Does raloxifene bind to sex hormone binding globulins (TeBG [a specific type of SHBG])? If so, will decreased levels of sex hormone binding globulins normally found in postmenopausal women result in significantly increased levels of free raloxifene?"

Binding interaction studies were carried out with ^{3}H-raloxifene in combination with ^{14}C-warfarin, ^{14}C-phenytoin, ^{3}H-tamoxifen, or raloxifene glucuronides. When these compounds were combined with raloxifene in plasma, no changes were observed in the percent binding of warfarin, phenytoin, or tamoxifen to plasma proteins. Nor did the addition of the raloxifene glucuronides affect the level of raloxifene bound to plasma protein. The glucuronide conjugates of raloxifene are not known to bind to the classic estrogen receptor *in vitro* and therefore, should not directly contribute to the pharmacology of raloxifene. However, the metabolites may function as prodrugs if they are hydrolyzed in vivo.

Both raloxifene and tamoxifen failed to displace ^{3}H-testosterone at concentrations as high as 10mM. All of the steroids displaced ^{3}H-

testosterone at concentrations of 10.7nM (testosterone), 113nM (estradiol), and 371nM (estrone). Since the maximal steady-state concentration of raloxifene is only approximately 10nM, raloxifene should not compete *in vivo* with endogenous sex steroids for binding to TEBG.

The following conclusions can be drawn:

1. Raloxifene is highly bound to plasma proteins.
2. Raloxifene has no effect on binding of warfarin, phenytoin, tamoxifen and raloxifene metabolites.
3. Raloxifene is not expected to compete with the sex steroids for TEBG.
4. The presence of the glucuronide conjugates had no effect on raloxifene binding to plasma proteins.

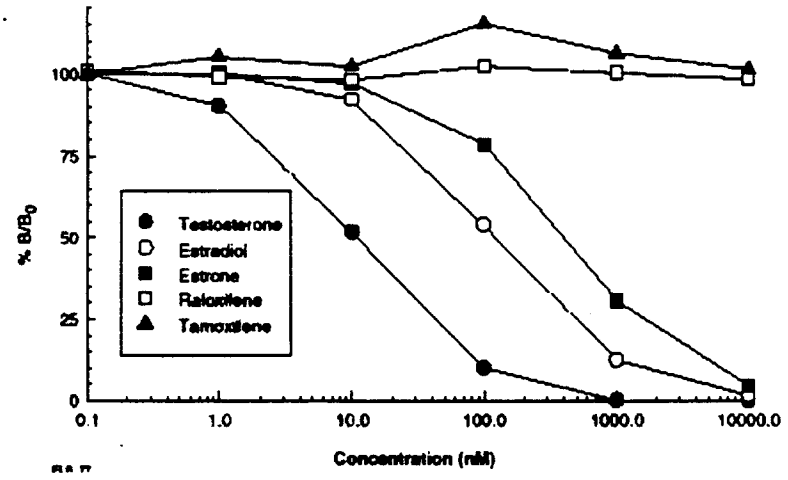

Figure 14 : Purified Human TeBG: Displacement of 3Testosterone Binding by Unlabeled Steroids & Anti-Estrogen Drugs

In vivo

(Gastrointestinal Drug Interaction)
Maalox

The objective of this study was to determine the effects of cholestyramine and antacid treatment on the pharmacokinetics of single doses of raloxifene HCl in fourteen healthy postmenopausal women, Single oral doses of raloxifene HCl (120 mg--2x 60 mg) were administered during cholestyramine therapy, antacid treatment, and control conditions in this nonblinded, randomized, three-way crossover study.

Commercially available antacid suspension containing Al(OH)3 and Mg(OH)2 was used in this study. The initial dose of 30 cc 4 times per day was administered in the first period to 4 subjects, two of whom developed antacid-induced diarrhea. The antacid dose was subsequently reduced to 15 cc 4 times per day for the remaining 9 subjects (one subject withdrew from the trial). The latter regimen provided approximately 400 mEq of acid neutralization per day. Antacid was administered

2 hours after each meal and at bedtime beginning the evening prior to raloxifene HCl dosing, and was continued through Day 3 of the blood sampling period. On the day of raloxifene HCl dosing, an additional 15 cc dose of antacid was administered 1 hour prior to raloxifene HCl, and the usual morning dose of antacid was given 2 hours following raloxifene HCl.

Table 21. Antacid Effect: Least Squares Mean and Confidence Intervals using Log-Transformed Data

Parameter [a]	Least Squares Mean [b] Antacid	Least Squares Mean [b] Control	Ratio of Means	90% Confidence Interval	p-value
Raloxifene					
C_{peak1}	0.410	0.423	0.97	0.75 to 1.25	0.84
AUC_{0-t}	35.1	31.0	1.13	0.92 to 1.39	0.32
Raloxifene-4'-glucuronide					
AUC_{0-t}	3982	2787	1.43	1.23 to 1.66	0.0005
Raloxifene-6-glucuronide					
AUC_{0-t}	966	669	1.44	1.16 to 1.80	0.0095

a Units for parameters: C_{peak1}, ng/mL ; AUC_{0-t} ng•hr/mL.

b Analyses of C_{peak1} and AUC_{0-t} parameters are based on log-transformed data so antilogs of transformed scale antacid minus reference differences and their 90% confidence limits supply an antacid/reference ratio estimate and corresponding 90% confidence interval. The point estimate of the ratio of equivalent means is 1.0.

The 13% increase in the extent of raloxifene systemic exposure following coadministration of antacid in this study (AUC_{0-t}) was not statistically significant. Changes in AUC_{0-t} of this magnitude are small when compared to the variability in plasma concentrations observed with this drug. The AUC_{0-t} of raloxifene-4'-glucuronide and raloxifene-6-glucuronide were significantly higher with antacid coadministration and the estimated increases for these two metabolites were 43% and 44%, respectively.

Cholestyramine

Cholestyramine was administered in the form of Questran Lite. Five gram packets containing 4 grams of anhydrous cholestyramine were reconstituted in water or juice per manufacturer's instructions. Cholestyramine therapy began 4 days prior to raloxifene HCl dosing, and was continued through Day 3 of the blood sampling period. On Day -4, one packet (5 gm) of cholestyramine was given orally in the morning. On Day -3, cholestyramine was increased to one packet orally twice a day (BID), and on Day -2, the dose was increased to two packets orally BID.

Raloxifene HCl and cholestyramine were administered at different times in this study. An *in vitro* binding experiment conducted prior to the initiation of this protocol demonstrated that

cholestyramine binds raloxifene and its conjugates extensively at relevant concentrations. The dosing regimen employed in this study was designed to avoid this direct interaction by administering cholestyramine 4 hours after raloxifene HCl administration. The second dose of cholestyramine on the day of dosing was administered prior to the second meal at approximately 10 hours after raloxifene HCl dosing.

Examination of the mean concentration-time profiles revealed that the reduction in systemic raloxifene exposure by cholestyramine occurred between 4 and 12 hours after raloxifene HCl dosing. This corresponded to the time of cholestyramine administration. The reduction in AUC by cholestyramine confirmed that raloxifene is enterohepatically cycled, and that peak plasma concentrations of raloxifene occurring between 4 and 12 hours after single doses of raloxifene HCl were probably due to the reabsorption of raloxifene from the gastrointestinal tract.

Administration of cholestyramine twice per day after a single dose of raloxifene resulted in a 40%, 46% and 32% reduction in the AUC_{0-t} of raloxifene, raloxifene-4'-glucuronide and raloxifene-6-glucuronide (Table 23). An initial peak raloxifene plasma concentration (Cpeak1), reflecting initial raloxifene absorption, was detected in all subjects and occurred most frequently at approximately 1 hour. Because this peak occurred so early, the sponsor should have collected a first blood sample at 15 or 30 minutes to adequately characterize the first peak.

Plasma raloxifene concentrations during cholestyramine therapy declined more rapidly between 4 and 12 hours after raloxifene administration. This period corresponded to the times of administration of cholestyramine prior to meals, and suggests that cholestyramine reduces enterohepatic cycling of raloxifene conjugates.

Table 23: Cholestyramine Effect: Least Squares Mean and Confidence Intervals using Log Transformed Data

Parameter [a]	Least Squares Mean [b]		Ratio of Means	90% Confidence Interval	p-value
	Cholestyramine	Control			
Raloxifene					
C_{peak1}	0.697	0.423	1.65	1.28 to 2.13	0.003
AUC_{0-t}	12.3	31.0	0.40	0.32 to 0.49	0.0001
Raloxifene-4'-glucuronide					
AUC_{0-t}	1273	2787	0.46	0.39 to 0.53	0.0001
Raloxifene-6-glucuronide					
AUC_{0-t}	211	669	0.32	0.25 to 0.39	0.0001

a Units for parameters: Cpeak1, ng/mL; AUC0-t, ng • hr/mL.

b Analyses of Cpeak1 and AUC0-t parameters are based on log-transformed data so antilogs of transformed scale cholestyramine minus reference differences and their 90% confidence limits supply a cholestyramine/control ratio estimate and corresponding 90% confidence interval. The point estimate of the ratio of equivalent means is 1.0.

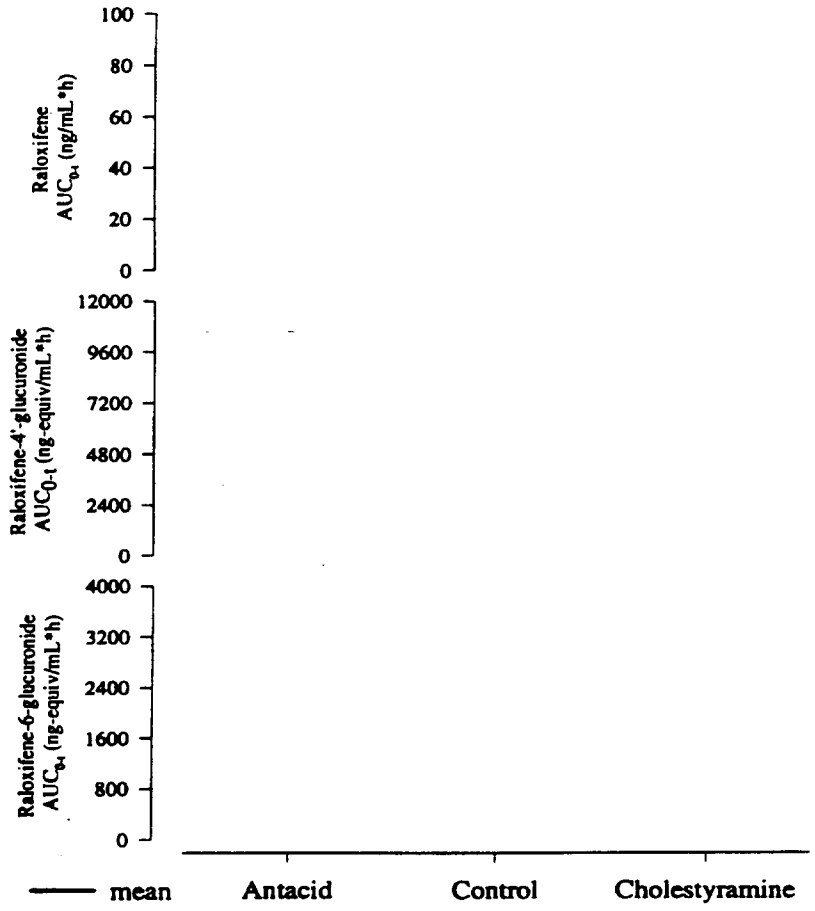

Figure 16: The effect of antacid and cholestyramine on the AUC_{0-t} of raloxifene, raloxifene-4'-glucuronide and raloxifene-6-glucuronide after single dose of 120 mg raloxifene HCL.

The following conclusions can be drawn from the above studies:

1. Administration of aluminum- and magnesium-hydroxide-containing antacids in doses typical of the treatment of peptic diseases did not alter the initial absorption (Cpeak1) or systemic exposure (AUC0-t) of raloxifene in this study.
2. Antacid therapy increased systemic exposure of metabolites.
3. Cholestyramine binds raloxifene and its metabolites at therapeutic concentrations.
4. Cholestyramine significantly affects the pharmacokinetics of raloxifene. Therefore, the drugs should not be coadministered.
5. An increase in side effect profile was observed with the treatment of the two gastrointestinal drugs. The effects were diarrhea and constipation which can be attributed to the antacid and binding agent. The occurrence of headaches was higher as well, with the coadministration of the drugs.

Warfarin

Single oral doses of warfarin (20 mg) were administered prior to and during a period of steady-state raloxifene dosing in a nonblinded, sequential, two-period study in fifteen healthy postmenopausal female subjects The pharmacokinetics of R- and S-warfarin

were characterized by blood sampling during a 120-hour period following warfarin dosing. The pharmacodynamics of a single dose of warfarin were characterized by measuring the prothrombin time during the same period. Repeated daily doses of raloxifene HCl (120 mg) were administered for a period of approximately eight drug half-lives. A second dose of warfarin (20 mg) was administered and measurements of warfarin pharmacokinetics and pharmacodynamics were repeated. Raloxifene HCl dosing was continued throughout the second warfarin sampling period. The sponsor separated warfarin administration by 15 days in an attempt to ensure adequate washout between doses. However, a residual concentration of R- and S- warfarin was detected in 12 and 4 subjects repectively.

The combined administration of warfarin and raloxifene resulted in a small (6% to 15%), but significant, increase in AUC0-∞ of warfarin enantiomers during raloxifene therapy, followed by a proportional decrease in the oral clearance. There was a small (<10%), but significant, decrease in volume of distribution for both R- and S-warfarin (Table 25). As a result of proportional changes in the clearance and volume of distribution, the half-life and mean residence time (MRT) remained unchanged.

Table 24: Least-Squares Means and Confidence Intervals of R- and S-Warfarin Pharmacokinetic Parameters, Warfarin Alone and in Combination with Raloxifene using Log-Transformed Data

	Least-Squares Mean				
Parameter [a]	Warfarin	Warfarin (+Raloxifene)	Ratio of means [b]	90% Confidence Interval	Significance p-value
R-Warfarin					
C_{max}	1667	1639	0.98	0.91 to 1.06	0.71
$AUC_{0-\infty}$	81340	86572	1.06	1.03 to 1.10	0.006
S-Warfarin					
C_{max}	1763	1659	0.96	0.86 to 1.06	0.47
$AUC_{0-\infty}$	49781	57371	1.15	1.09 to 1.21	0.0002

[a] Units for parameters: C_{max} (ng/mL) and $AUC_{0-\infty}$ (ng•hr/mL).

[b] Analyses of C_{max}, and $AUC_{0-\infty}$ parameters are based on log-transformed data. Antilogs of transformed scale warfarin+raloxifene minus warfarin differences and their 90% confidence limits supply a ratio estimate and corresponding 90% confidence interval. The point estimate of the ratio of equivalent means is 1.0.

APPEARS THIS WAY
ON ORIGINAL

Table 25: Least-Squares Means and Confidence Intervals of R- and S-Warfarin Pharmacokinetic Parameters, warfarin Alone and In Combination with Raloxifene using Nontransformed Data

Parameter [a]	Least-Squares Mean: Warfarin	Least-Squares Mean: Warfarin (+Raloxifene)	Difference in means (%) [b]	90% Confidence Interval (%)	Significance p-value
R-Warfarin					
λ_z	0.02	0.02	2.1	-3.7 to 8.0	0.53
CL_P/F	2.16	2.01	-7.1	-12.9 to -1.2	0.05
V_{SS}/F	8.32	7.71	-7.4	-11.9 to -2.8	0.01
S-Warfarin					
λ_z	0.02	0.02	1.3	-4.1 to 6.6	0.68
CL_P/F	3.54	3.04	-14.1	-21.0 to -7.2	0.003
V_{SS}/F	9.01	8.13	-9.8	-14.2 to -5.3	0.002

[a] Units for parameters: λ_z (hr^{-1}); CL_P/F (L/hr); V_{SS}/F (L).

[b] Warfarin+raloxifene minus warfarin differences in least-squares mean values are expressed as a percentage of the warfarin reference value. The point estimate of the difference in equivalent means is 0.0%.

The mean prothrombin time before warfarin dosing was not different from baseline during raloxifene therapy. The maximum prothrombin time after a single dose of warfarin (20 mg) was reduced by 10% during raloxifene therapy. The AUC_{PT} of the pharmacodynamic effect was similarly reduced by 8% under these conditions (Table 26). The effect of raloxifene on the pharmacodynamics of warfarin is not accounted for by changes in warfarin pharmacokinetics, which were in the opposite direction. The sponsor noted that this observance could be related to the estrogen agonist effect of raloxifene. Estrogens are known to increase plasma concentrations of Vitamin K-dependent clotting factors.

Table 26: Least-Squares Means and Confidence Intervals of Prothrombin Time (PT), Warfarin Alone and in Combination with Raloxifene using Log-Transformed Data

Parameter [a]	Least-Squares Mean: Warfarin	Least-Squares Mean: Warfarin (+Raloxifene)	Ratio of means [b]	90% Confidence Interval	Significance p-value
Prothrombin					
PT_b	10.98	10.94	1.00	0.98 to 1.01	0.73
PT_{max}	19.6	17.6	0.90	0.87 to 0.93	0.0001
AUC_{PT}	1888	1742	0.92	0.90 to 0.94	0.0001

[a] Units for parameters: PT_b = baseline PT (sec); PT_{max} = maximal PT after warfarin (sec), and AUC_{PT} (sec•hr).

[b] Analyses of PT_b, PT_{max} and AUC_{PT} parameters are based on log-transformed data. Antilogs of transformed scale warfarin+raloxifene minus warfarin differences and their 90% confidence limits supply a ratio estimate and corresponding 90% confidence interval. The point estimate of the ratio of equivalent means is 1.0.

The effect of raloxifene on prothrombin time is difficult to assess in this particular study because it was a single dose study that used doses of warfarin significantly larger than what is seen in a clinical setting of chronic therapy. Also, the accumulation of warfarin under multiple dose conditions has not been assessed with this current study design and warfarin should be evaluated in a multiple dose study because of conflicting data. Therefore, the reviewer is not in agreement with the sponsor's inference that raloxifene has no real effect on warfarin pharmacokinetics/ pharmacodynamics. Because of the narrow therapeutic index of this drug, caution should be used in making assumptions regarding the behavior of this drug.

The following conclusions can be made:

1. Due to the study design, the warfarin pharmacodynamics were not adequately assessed.
2. Conflicting information was generated which substantiates the need for further evaluation.

Digoxin

Twenty-four healthy male subjects, years participated in a randomized, double-blind, parallel study comprising of two periods of treatment. After loading doses of 2 x 0.5 mg digoxin on Day 1, all subjects received 0.375 mg digoxin daily for 15 days. On Day 6, subjects were randomized to receive either raloxifene or placebo in addition to digoxin until the end of study (Day 16). Raloxifene HCl was administered in the amount of 120 mg (2 x 60-mg tablets) twice daily from Day 6 to Day 9 and once daily thereafter in order to achieve plasma concentrations typical of steady-state values during chronic therapy.

Using the 90% confidence interval criteria as an evaluation of drug interaction, there was no effect

on digoxin as a result of coadministration with raloxifene. When comparing vital signs and EGC parameters at pre- and poststudy, no statistical difference was observed except for a statistically significant decrease of weight and heart rate in ECGs (but not in pulse rate) in the raloxifene group. Also, a slight but statistically significant decrease in cholesterol was noted and thought to be compatible with the known pharmacological effects of raloxifene.

Table 27: Pharmacokinetic Interaction of Digoxin After Repeated Administration Of Raloxifene

		Least Square Means (covariance adjusted)				t-test[c]
PK Parameters[a]	Overall Mean Day 5	Placebo (P)	Raloxifene (R)	R/P (%)	R/P C.I[b]	p-value
$AUC_{(0-24\ h)}$	28.7571	27.8679	29.6678	106.459	99.9 - 113.5	0.1072
Cl_{tot}/F	13.2458	13.7411	12.8589	93.580	86.7 - 100.5	0.1242
C_{max}	3.0114	2.8951	3.3010	114.019	105.0 - 123.8	0.0119 *
C_{min}	0.9206	0.9181	0.9701	105.670	97.6 - 114.5	0.2480

[a] AUC in µg*h/l; Cl_{tot}/F in l/h; C_{min} (mean of C_0 and $C_{24\ h}$) and C_{max} in µg/l
AUC, C_{max} and C_{min} data have been log-transformed prior to be analyzed.

[b] 90 % confidence interval of the means expressed in % of the placebo mean.

[c] t-test for equality of the means.

* indicates statistical significance ($p < 0.05$).

The following conclusion was made:

1. Digoxin and raloxifene can be coadministered.

VII. Pharmacodynamics

Raloxifene is a compound which possesses antiestrogenic activity and it is this mechanism of action that is used for the indication of osteoporosis. It is believed to act by the same mechanism as tamoxifen, though the structures and pharmacological activity are different. Eighteen healthy male subjects, participated in a 21-day, open-label study that was conducted to determine the effects of oral administration of raloxifene (4 x 50 mg capsules) and tamoxifen (2 x 50 mg capsules) on estrogen-induced changes in anterior pituitary hormones (prolactin, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), sex steroids (testosterone and estradiol), and binding globulins (thyroid binding globulin [as represented by T3 resin uptake or T3 RU], transcortin, and sex steroid binding globulin). Before, during, and after administration of these agents, plasma levels of anterior pituitary hormones, sex steroids, and binding globulins were measured.

Minimal pharmacokinetic analyses were conducted. The parent drug levels were below the limit of quantitation (<10 mg/mL). However trough levels of the conjugated metabolites were measured. In all cases, to varying degrees, antiestrogenic properties were exhibited by both raloxifene and tamoxifen. In most cases, the effects were magnified with tamoxifen. The only endocrine markers which raloxifene and tamoxifen had no effect on were transcortin and sex steroid binding globulin.

In another study, the short-term effects of raloxifene on reproductive endocrine function in healthy women of reproductive age as measured in the production of pituitary gonadotropins and ovarian steroids, follicular maturation, corpus luteum function and endometrial development were evaluated. The pharmacokinetics of raloxifene was also determined and the potential relationships of the drug and its metabolite concentrations with changes in estradiol (E2), progesterone, prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) concentrations compared with control menstrual cycles (prior to raloxifene therapy) were explored.

The pharmacodynamic results showed that estradiol increased when raloxifene was administered during the follicular phase, however, there was no correlation between the respective AUCs. Furthermore, the AUC of prolactin, LH and FSH were not altered by raloxifene therapy. Raloxifene is sensitive to the time of administration of the doses relative to the menstrual cycle. A 2 x increase in pharmacokinetic parameters is observed in the ovulatory phase. However, TRHP and the conjugates are more sensitive to the luteal phase of the menstrual cycle.

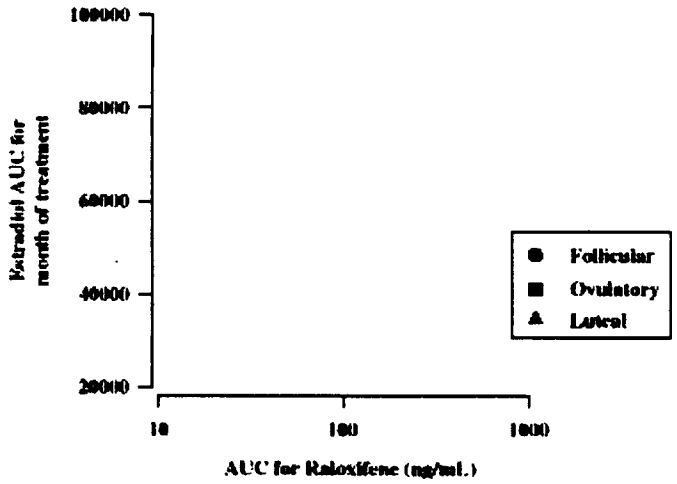

Figure 17: Estradiol AUC versus Raloxifene AUC.

A NONMEM analysis showed that clearance was statistically significantly influenced by treatment phase of the menstrual cycle. The model of predicted vs. observed concentration concurred at lower concentrations. However, deviations from unity began to occur at 6 ng/mL. This phenomenon could not be truly assessed because of high within-subject variability, small sample size and lack of crossover of the subjects.

Therapy with raloxifene HCl 30, 60, and 150 mg/day resulted in statistically significant clinical changes in total body, total hip, and lumbar spine BMD; biochemical markers of bone metabolism; and in total cholesterol and LDL-C. The changes showed a minor correlation to dosage. However, the greatest changes were between 30 mg and the higher two dosages. No apparent relationship existed between the 60 mg and 150 mg dosages. There were no statistically significant differences among the therapy groups in the incidence of serious adverse events.

The following conclusions can be drawn:

1. Raloxifene exhibits anti-estrogenic activity on various anterior pituitary hormones, sex steroids and thyroid binding globulins.
2. Estradiol increases with raloxifene.
3. Raloxifene causes significant clinical changes that have a small correlation to dose.

VIII. Population Pharmacokinetics

Population pharmacokinetic analyses of data from 8 clinical pharmacology studies of raloxifene have been conducted. The objectives of these evaluations included developing compartmental pharmacokinetic models for raloxifene and TRHP and determining if dose and subject age affect raloxifene disposition. Additional work was done to investigate the interconversion of raloxifene and its glucuronides by developing composite compartmental models. These analyses were accomplished with a nonlinear, mixed-effects modeling program (NONMEM). The blood sampling from these studies was frequent (e.g., pre-dose, 0.5, 1, 3, 4, 5, 6, 9, 12, 24 hr, ...5-6 days).

Analyses included both one- and two-compartment models with a first-order rate for raloxifene appearance and first-order elimination from the central compartment (V) as well as various models for the inter-individual and residual error structure. Absolute bioavailability of an oral raloxifene dose (F_{abs}) and dose fraction appearing in the systemic circulation as TRHP (F_{app}) were held constant at 1.99% and 63.3%, respectively.

The pharmacostatistical model that adequately described the data incorporated a one-compartment model with first-order rate of *appearance* and first-order elimination from the central compartment, a constant coefficient of variation (CCV) error model for the inter-individual variability in the pharmacokinetic parameters of ka, CL, and V, and a CCV error model for the random residual variability. The NONMEM first-order conditional estimation (FOCE) method was used.

The population pharmacokinetic parameters generated through the final base model (no covariates) are listed in Table 28. NONMEM and noncompartmental parameters from each of 4 studies were comparable.

Table 28. One-compartment Single-dose POP PK Parameters for Raloxifene[a]

Parameter	Estimate (%SEE)[b]	Between-subject Variability (%SEE)
ka (hr^{-1})	0.561 (11.4)	91% (21)
CL (L/hr)	48.6 (5.2)	42% (18)
V (L)	3260 (5.4)	46% (18)
Residual error	34% (4.7)	

[a] 2196 observations in 79 healthy postmenopausal subjects.
[b] Standard error of the estimate expressed as % of the estimate.

It is known that raloxifene undergoes entero-hepatic recirculation (EHR). Although the final model did not account for EHR, it provided a reasonable estimate of the pharmacokinetic profile of raloxifene. From 'observed raloxifene concentration vs. predicted raloxifene concentration' plots it is evident that the model under predicts concentrations above approximately 1 ng/mL; this might be expected since the terminal phase of the predicted profile can only decline while EHR results in multiple late observed peaks.

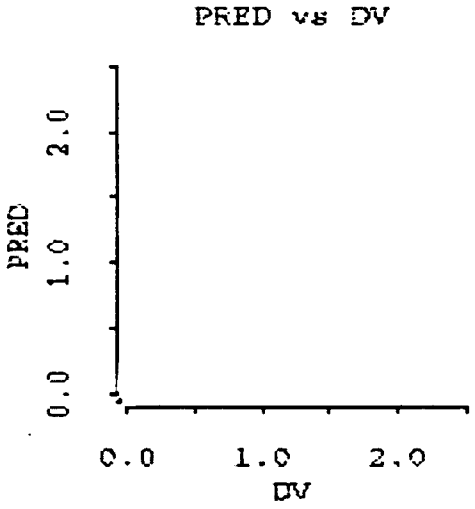

Figure 18: Observed vs. Predicted Raloxifene Concentrations

The precision of the parameter estimates was high with the SEE approximately and between-subject and residual variability SEE 21% or less. Between-subject variability in ka was high and may reflect the multiple processes (e.g., initial absorption, first-pass metabolism, EHR) involved in the appearance of raloxifene in plasma.

The effect of dose (60, 120, 150 mg) on bioavailability was evaluated. It was determined that the 60 mg dose was not different from the 120 mg dose. However, the 150 mg dose was about 20% less bioavailable compared to the other two doses. The effect of age (median, range: 64, 45-84) on pharmacokinetic parameters was investigated and was found to have no significant effect on ka, CL, or V. Inter-occasion variability (e.g., variability with-in a subjects dosed on more than one occasion) was determine to be 42% for ka, 17% for V, and negligible for CL.

A similar analysis was conducted for TRHP, with results listed in Table 29. A similar model as raloxifene was used. Parameter and variability SEE are larger than for raloxifene. The blood sampling schedule may factor into the poorly estimated ka, since blood samples were first collected

at 0.5 hr but the 'appearance half-life' [Ln(2)/ka] is about 7 minutes; therefore, ka could not be well characterized.

Table 29. One-compartment Single-dose POP PK Parameters for TRHP[a]

Parameter	Estimate (%SEE)[b]	Between-subject Variability (%SEE)
ka (hr^{-1})	6.07 (21)	151% (55)
CL (L/hr)	12.5 (11.5)	58% (22)
V (L)	444 (8.5)	38% (30)
Residual error	56% (53)	

[a] 537 observations in 28 healthy postmenopausal subjects.
[b] Standard error of the estimate expressed as % of the estimate.

The sponsor investigated multi-compartmental models that co-modeled raloxifene and TRHP, as well as models that accounted for interconversion of the three glucuronide metabolites. However, these models were exploratory and not used to support any labeling. In addition, according to the sponsor, the combined raloxifene/TRHP pharmacokinetic model was not pursued due to run times longer than 10 days. As such, this research effort will not be reviewed here.

The sponsor used NONMEM to explore the potential impact of various covariates from efficacy trials on raloxifene pharmacokinetics. The one-compartment pharmacokinetic models for raloxifene and TRHP developed from the clinical pharmacology data were applied to the sparse pharmacokinetic data (e.g., 3, 6, 12, 18, and 24 month) collected during the first 24 months of 3 clinical phase 3 prevention studies, as well as 3 phase 2 treatment studies (6 or 12 months). The final NONMEM data set used for the various analyses included data from 1350 patients with 10881 observations (raloxifene and TRHP concentrations). Doses in these studies were 30, 60, 120, or 150 mg/day. Although some covariates tested (e.g., self-reported smoking status, dose, duration of therapy, estimated creatine clearance, total bilirubin and weight) were identified as significant covariates in the final population pharmacokinetic model for raloxifene and/or TRHP, no covariate (including age and race) was identified that had a significant impact on raloxifene pharmacokinetics.

Typically, to validate a NONMEM model, a validation data set (i.e., a data set excluded from developmental models and later used to test the prediction ability of the final model) is used. These NONMEM analyses did not utilize such a validation procedure. Instead, separate analysis was done for each study and for various combinations of studies with comparison of results. Also, NONMEM and noncompartmental analysis from many of the clinical pharmacology studies were

found to give comparable parameter estimates. There was much work done to investigate covariate effects on the pharmacokinetics of raloxifene, but little of it is reflected in the labeling. The labeling claims the sponsor is making, based on the NONMEM analyses, pertain to age and race. The model used is adequate to describe the pharmacokinetics of raloxifene, although it does not incorporate EHR. The consistency between analyses (NONMEM to NONMEM as well as NONMEM to noncompartmental) supports the results. Also, the consistency that no differences in raloxifene pharmacokinetics were detected in any NONMEM analysis with respect to age supports this labeling claim.

The labeling claim ("no discernible differences in raloxifene pharmacokinetics among" races) includes the proportion of races in the data set. Most (93.5%) were Caucasian and, thus, it is not surprising that no differences were found. The occurrence of osteoporosis in some minority populations, especially African-Americans is small. Even still, the evaluation of 5 subjects to make a determination regarding pharmacokinetic differences is not adequate. The population study included 12 Asian subjects in the data set. Which again represents insufficient numbers. However, the sponsor did conduct several classical pharmacokinetic studies in the Japanese population but the full study reports were not included in the submission. Therefore, no additional information could be incorporated into the label (see labeling comments).

The following comments can be made:

1. The sponsor conducted a tremendous amount of analyses. However, only two issues were addressed in the label.
2. Age has no effect on raloxifene pharmacokinetics.
3. Race cannot be effectively evaluated because of the small amount of subjects in the trials from ethnic groups other than Caucasian. Although, the sponsor has conducted classical pharmacokinetic studies in the Japanese population a complete study report was not submitted to the Agency. Therefore a cross-study comparison between the two groups cannot be conducted. Therefore, no statement regarding race can be used in the label.

COMMENTS FROM THE MEDICAL OFFICER REGARDING THIS SUBMISSION:

The Medical Officer, Dr. Colman states that raloxifene shows marginal (2%) improvement in bone mass density. Estrogen which is the current therapy for the prevention and treatment of osteoporosis is 5x more efficacious. One major question is, Does this BMD increase translate to an improvement in fracture data?

The second issue is, what does the animal bone strength data indicate?

Lastly, Dr. Colman feels the sponsor is interested in marketing the fact that the incidence of breast cancer is decreased in patients who are taking raloxifene. However, the oncology group is not comfortable with a label claim at this time because not enough information in available.

At this point the medical officer is undecided about the approvability of this drug and believes more information is required before a decision can be made.

COMMENTS TO BE SENT TO THE FIRM:

2. In regards to hepatic insufficiency, if the sponsor is planning additional studies at the 150 mg dose, then raloxifene pharmacokinetics should be evaluated at this higher dosage in more severely impaired patients.

3. In the future, independent of raloxifene, when designing drug interaction studies, the sponsor should look at the interaction in both directions: The effect of Drug A on Drug B and the effect of Drug B on Drug A.

LABELING COMMENTS:

1. The sponsor makes a statement regarding the concomitant administration of certain classes of medications during the clinical trials. If a sub-group analysis has not been conducted and if sufficient number of subjects have not been exposed to these drugs, the section on OTHER CONCOMITANT THERAPY should not be allowed in the package insert. If a subgroup analysis has been conducted, it should be submitted to the Agency for review.

2. Under the heading of Special Populations the term "Geriatric" is used in reference to a population which includes subjects under the age of 65. Is this correct? The age range in all NONMEM analyses was 42 to 84 years. Therefore, the label should be changed from 83 to 84 years of age.

Carolyn D. Jones

APPEARS THIS WAY
ON ORIGINAL

9/26/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 10/9/97
OCPB Briefing: (10/16/97; Balian, Huang, Chen, Ahn, Shore, Baweja, Jenkins)
FT initialed by Hae-Young Ahn, Ph.D., Team Leader 10/23/97
cc: NDA 20-815 (1 copy) HFD-510 (Colman, Hedin), HFD-340 (Vishwananthan), HFD-870 (Ahn, Jones, M. Chen), CDR (Murphy).

"CM"

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815

ADMINISTRATIVE DOCUMENTS

RALOXIFENE HYDROCHLORIDE

NDA 20-815

ITEM 13: PATENT INFORMATION

The undersigned declares that the following patents cover raloxifene, through formulation, compound, method of use, and/or other claim types. This product is the subject of this application for which approval is being sought:

Patent Number	Expiration Date	Claim Type(s)
4,418,068	April 3, 2003	Compound, pharmaceutical composition, method of use
5,393,763	July 28, 2012	Method of use
5,457,117	July 28, 2012	Method of use
5,478,847	March 2, 2014	Method of use
5,641,790	June 24, 2014	Pharmaceutical formulation, method of use

The above patents are all owned or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

ITEM 14: PATENT CERTIFICATION

Eli Lilly and Company (Lilly) claims a five year period of exclusivity for the use of raloxifene as provided by 21 C.F.R. 314.108(b)(2). As evidenced by the absence in the Orange Book that raloxifene has previously been approved by the FDA, to the best of Applicant's knowledge and belief, raloxifene has not previously been approved under section 505(b) of the FFDCA. Accordingly, Lilly submits raloxifene is a new chemical entity entitled to a five year period of exclusivity as provided by FFDCA 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii)(21 U.S.C. 355(c)(3)(D)(ii) and 355(j)(4)(D)(ii)).

EXCLUSIVITY SUMMARY for NDA # 20-815 **SUPPL #** _____

Trade Name Evista **Generic Name** raloxifene hydrochloride

Applicant Name Lilly **HFD-** 510

Approval Date _____

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 /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) 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.

   _____

   _____

   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:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

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

5 yrs.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 ON PAGE 8 (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.

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).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 ON PAGE 8.

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 BLOCK ON PAGE 8:**

_____

_____

(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:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) 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 #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ 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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2 YES /___/ Explain _____ _____ _____	NO /___/ 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: _____

_____

_____

_____

_____ 11/17/97
Signature Date
Title: Senior Regulatory Management Officer

_____ 12/3/97
Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

DEBARMENT CERTIFICATION

NDA Application No: 20-815.

Drug Name: Raloxifene Hydrochloride.

Pursuant to provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Jennifer L. Stotka, M.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.335(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Jennifer L. Stotka, M.D.

APPEARS THIS WAY
ON ORIGINAL

Title: Director
U.S. Regulatory Affairs

Date: 2 June 1997

APPEARS THIS WAY
ON ORIGINAL

(To be completed for all NME's recommended for approval)

NDA # 21-815 Trade (generic) names Evista (raloxifene hydrochloride) tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

4. The indication is for the prevention of bone loss in postmenopausal women and therefor would not be used in children.

Signature of Preparer

11/17/97
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

DEC - 2 1997

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

DATE: December 1, 1997

TO: Randy Hedin
DMEDP

FROM: Carolyn D. Jones, Ph.D.
OCPB/DPEII

RE: Additional Labeling Changes for NDA 20-815 EVISTA® (Raloxifene)

Meeting date: November 26, 1997

SYNOPSIS:

During the labeling meeting the following two requests were made to OCPB for labeling changes:

1. Addition of language under the drug-drug interaction section regarding cyclosporine and corticosteroids, two drugs that have the potential to be commonly prescribed with raloxifene (p.16 Label dated 11/21/97).

> Cyclosporin: The coadministration of raloxifene with cyclosporine has not been evaluated.
>
> Corticosteroids: The coadministration of raloxifene with corticosteroids has not been evaluated.

2. In the label, mention some of the highly bound protein drugs that caution should be used when coadministered with raloxifene (p. 21 Label dated 11/21/97).

> Examples of highly protein bound drugs that have the potential of being commonly prescribed with raloxifene are: clofibrate, indomethacin, naproxen, ibuprofen, warfarin, diazepam, and diazoxide.

cc: NDA 20-815, HFD-510 (Colman, Hedin), HFD-870 (M. Chen, Ahn, Jones), CDR (Murphy).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-815

JUN 12 1997

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Evista (raloxifene hydrochloride) Tablets, 60 mg.

Therapeutic Classification: Priority

Date of Application: 8 June 1997

Date of Receipt: 9 June 1997

Our Reference Number: NDA 20-815

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 8, 1997, in accordance with 21 CFR 314.101(a).

We note your request under 21 CFR 314.102(c) of the new drug regulations for an informal "90 day" conference with this Division for a brief report on the status of the review (but not on the application's ultimate approvability), and we will contact you soon with possible dates. Should you have any questions concerning this NDA, please contact Randy Hedin, R.Ph., Consumer Safety Officer, at (301) 443-3520.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

emg 6-12-97

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-815 (+ a#.)
HFD-510/Div. Files
HFD-510/CSO/R.Hedin
HFD-510/SSobel/GTroendle/EColman/RSteigerwalt/DWu/
DISTRICT OFFICE

Drafted by: emg/June 11, 1997/\20815ac.nda
Final: emg/6.12.97

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

NDA 20-815

MAR 17 1997

Eli Lilly and Company
Attention: Jennifer Stotka, M.D.
Director
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

We have received your pre-submission of the nonclinical pharmacology and toxicology section for the following:

Name of Drug Product: Evista (raloxifene hydrochloride) Tablets 60 mg

Date of Application: March 13, 1997

Date of Receipt: March 17, 1997

APPEARS THIS WAY
ON ORIGINAL

Our Reference Number: 20-815

We will review this early submission as resources permit. We will not, however, consider it subject to a review clock or to a filing decision by FDA. If you have any questions regarding this information, please contact Mr. Randy Hedin, Senior Regulatory Management Officer, at 301-443-3520.

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no later than 120 days from the date of your submission.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

EMG 3-17-97

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-815
HFD-510/Div. Files
HFD-510/CSO/R.Hedin
HFD-510/GKuijpers/RSteigerwalt
DISTRICT OFFICE

Drafted by: RH/March 17, 1997/N20815M.LT1
Final:

ACKNOWLEDGMENT (M)

APPEARS THIS WAY
ON ORIGINAL