

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020815, S003**

**ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS**

## 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 currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act:

<u>Patent Number</u>	<u>Expiration Date</u>	<u>Claim Type(s)</u>
4,418,068	April 3, 2001	Compound, Pharmaceutical Composition
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
5,731,327	March 24, 2015	Compound, Pharmaceutical Formulation
5,731,342	January 27, 2017	Pharmaceutical Formulation
5,747,510	March 2, 2014	Pharmaceutical Formulation
5,811,120	March 2, 2014	Pharmaceutical Formulation

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

## EXCLUSIVITY

Eli Lilly and Company (Lilly) claims a three year period of exclusivity for the use of Evista® in the treatment of osteoporosis in postmenopausal women, as provided by 21 C.F.R. 314.108(b)(5).

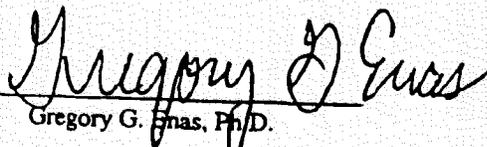
Clinical trials conducted which are essential to approval of this supplemental NDA are identified as follows:

H3S-MC-GGGN  
H3S-MC-GGGP  
H3S-MC-GGK

As required by 21 C.F.R. 314.50(j)(4), Lilly certifies that to the best of Lilly's knowledge:

- each of the above clinical investigations included in this supplemental application meets the definition of "new clinical investigation" as set forth in 21 C.F.R. 314.108(a);
- the above clinical investigations are "essential to approval" of this supplemental application. Lilly, through its employees and others, electronically searched the Scientific literature as of December 31, 1998 via Medicine, Ringdoc, and World Patents Index and has not discovered any published or publicly available reports for which Lilly is seeking approval. In Lilly's opinion and to the best of Lilly's knowledge, there are no published studies or publicly available reports to provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the new clinical investigations in this application.
- the above clinical investigations were each conducted or sponsored by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND number \_\_\_\_\_ (active as of June 26, 1992 under which the new clinical investigations that are essential to the approval of this application was conducted.

ELI LILLY AND COMPANY

By:   
Gregory G. Enas, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: March 30, 1999

EXCLUSIVITY SUMMARY FOR NDA # 20-815/S-003 SUPPL # 003

Trade Name Evista

Generic Name Raloxifene

Applicant Name Lilly

HFD # 510

Approval Date If Known \_\_\_\_\_

**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 question 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.)

SE1

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? 3

e) Has pediatric exclusivity been granted for this Active Moiety?

No

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? (Rx to OTC switches should be answered NO-please indicate as such)

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# 20-815 \_\_\_\_\_

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.

(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:

H3S-MC-GGGN      H3S-MC-GGGK  
H3S-MC-GGGP

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.



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"):

H3S-MC-GGG-N     H3S-MC-GGG-K  
H3S-MC-GGG-P

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: \_\_\_\_\_

IND  <sup>#3</sup> YES

(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 \_\_\_\_\_

\_\_\_\_\_  
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: \_\_\_\_\_  
\_\_\_\_\_

                    / S /                      
Signature

Title:                     CSO                    

                    9/23/99                      
Date

                    / S /                      
Signature of Division Director

                    9/29/99                      
Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

### PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

<b>NDA/BLA Number:</b>	<u>20815</u>	<b>Trade Name:</b>	<u>EVISTA (RALOXIFENE HCL)</u>
<b>Supplement Number:</b>	<u>3</u>	<b>Generic Name:</b>	<u>RALOXIFENE HCL</u>
<b>Supplement Type:</b>	<u>SE1</u>	<b>Dosage Form:</b>	<u>TAB</u>
<b>Regulatory Action:</b>	<u>PN</u>	<b>Proposed Indication:</b>	<u>The treatment of osteoporosis in postmenopausal women.</u>

**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**            Adequate for ALL pediatric age groups  
**Formulation Status**       -  
**Studies Needed**            -  
**Study Status**               -

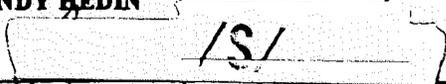
**Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission?** NO

**COMMENTS:**

This drug is a selective estrogen receptor modulator used to treat postmenopausal osteoporosis, and it's use in children would be contraindicated.

This drug is a selective estrogen receptor modulator used to treat postmenopausal osteoporosis, and it's use in children would be contraindicated.

**This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN**

  
 \_\_\_\_\_  
 Signature

9/24/99  
 \_\_\_\_\_  
 Date

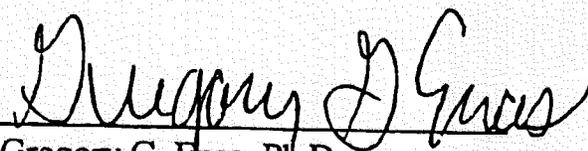
**DEBARMENT  
CERTIFICATION**

NDA Application No.: 20-815

Drug Name: 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 G. Enas, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: March 30, 1999

**Claim for Categorical Exclusion from the Requirement for an Env. Assessment**

Eli Lilly and Company claims the categorical exclusion from the requirement for an environmental assessment to support the approval of Evista for the treatment of postmenopausal osteoporosis. The active ingredient in Evista is raloxifene hydrochloride.

The final rule for revision of policies and procedures pertaining to the National Environmental Policy Act used by the Food and Drug Administration was published in the Federal Register (July 29, 1997). Section 21CFR 25.31(b) provides for a categorical exclusion from the requirement for an environmental assessment for a new drug application if the estimated concentration of the substance at the point of entry into the aquatic environment will be [redacted] of raloxifene hydrochloride is expected to be used in the United States annually for all indications. The daily discharge of water from sewage treatment facilities in the United States is about  $1.115 \times 10^{11}$  liters. The maximum concentration of raloxifene hydrochloride that may be discharged into the aquatic environment would be less than [redacted] assuming no reduction of raloxifene hydrochloride at the sewage treatment facility.

All information available to Eli Lilly and Company indicates that no extraordinary circumstances exist as specified in section 21CFR 25.21 for the approval of this new drug application. No information exists which establishes that, at the expected level of exposure, there is potential for serious harm to the environment. No information exists which establishes that endangered or threatened species would be harmed.

Based on this information, Eli Lilly and Company claims a categorical exclusion from the requirement for an environmental assessment.

0.11  
REFERER NOS

0.12  
SUMMARY OF INDEX

0.13  
TOC

*Categorical Exclusion  
from Environmental  
Assessment is deemed  
SATISFACTORY  
SAN 4-20-79*

*Concurred.*

*[Signature Box] 9/28/99*

# MEMORANDUM

DEPARTMENT OF HEALTH AND  
HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** 09/29/99

**FROM:** Lisa Rarick, M.D. 151  
Director  
Reproductive and Urologic Drug Products, HFD-580

**SUBJECT:** Consult review of NDA 20-815 regarding endometrial polyps

**TO:** Sol Soebel, M.D.  
Director  
Division of Metabolic and Endocrine (HFD-510)

Please see the attached review prepared by Dr. Gerald Willett from this Division

**cc:**  
HFD-580/Controlled Correspondence (DRUDP-68b) + incoming

APPEARS THIS WAY  
ON ORIGINAL

NDA 20-815 Evista (raloxifene)

Second consultation report for HFD-510 from Dr. Willett (HFD-580) in regard to endometrial polyps.

I have received the additional requested material from Lilly to aid in my analysis of endometrial polyps found in their study. I have previously discussed some of the difficulties in fully analyzing the data. These included:

1. Lack of complete longitudinal sonographic studies in the entire patient cohort.
2. The reliance in some cases on local pathology determinations as opposed to a central reading of all biopsies.
3. The inclusion of patients who took additional hormones during the study.
4. The difficulties of histologic diagnosis of polyps in material derived by pipelle aspiration.

Lilly sent additional information on the sonographic and pathologic protocols, more detailed pathology information on the patients where sonographic measurements were recorded and some additional information on patients with cervical polyps.

I took all the polyp information and tabulated the results in regard to bleeding, medication level or placebo, additional hormones, biopsy procedure, pathology reading, and sonographic measurements of the endometrial thickness. I then established different groupings that might help establish whether there may be some relation to polyp formation.

Endometrial polyps are thought to arise from estrogen stimulation of basal endometrium. Very few polyps are found to have secretory change and thus progesterone is not felt to be contributory. Some recent research has indicated some possible genetic alterations that may predispose to the condition (inversions). Selective estrogen receptor modulators such as tamoxifen have been shown to have an increased number of polyps.

Though atypical hyperplasia and cancer can arise within a polyp, this event is rare. The information on raloxifene shows no increase in endometrial cancer above placebo.

I have not performed any statistical analysis of the numbers I derived in my separate groupings. Though endometrial polyps appear to be occurring more often in the treated group, I do not know if there is any statistical significance. I did not see anything concerning in my review of the cervical polyp data.

/S/

Gerald Willett MD  
HFD 580

/S/

9/22/95