2. Sponsor's Current Proposal

Currently the sponsor proposes that:

- The above statement be deleted from the "Precautions" section of the label
- The "modified" statement below be included in the "Adverse Reactions" section under the heading "Additional Safety Information"

The sponsor cites the following in support of the new "modified" statement above

3. Comments

- Instead of deleting the original statement about cognition and affect altogether from the label as recommended by this Division, the sponsor has merely moved the statement, with no meaningful change, from one section of the label to another
- The results of Study GGGK have earlier been reviewed in detail by me (see my review of 7/16/99); we have already concluded that, on account of multiple deficiencies in that study, the results cannot be used to support the sponsor's contention that raloxifene does not have a deleterious effect on cognition and affect
- I would recommend that the new "modified" statement also be deleted from the label

Ranjit B. Mani, M.D.
Medical Reviewer

R. Levin, M.D. _____

rbm 9/16/99
cc:
HFD-120
HFD-510
Division Consult File
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COMPLETED JUL 2 0 1999

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neuropharmacological Drug Products (HFD – 120)
Center for Drug Evaluation and Research

Date: 7/19/99

From: Russell G. Katz, M.D. /S/ 7/20/99
Acting Division Director

To: Solomon Sobel, M.D.
Division Director
Division of Metabolic and Endocrine Drug Products (HFD – 510)

Subject: NDA 20-815/S-003

Document Type: Consult

Enclosed is the Division's response to your request

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AUG 1 6 1999

I agree with Dr. Mani that the sponsor has not provided sufficient evidence to support the claim that the drug is not associated with deterioration of cognitive function or affect and that any change with use is unlikely related to therapy. I do agree that cognitive or affect changes should be investigated as clinically indicated though that can be said for just about any adverse event with any drug and it is not necessary to put this statement in labeling.

In study GGGK, which was evaluating the effect of the drug on prevention of dementia as a secondary outcome measure, failed to show that the drug prevented dementia since not even placebo patients developed dementia. This study cannot be used to support the sponsor's claim regarding cognitive function in otherwise healthy subjects. The study and the scales used were not designed to assess the cognitive function of non dementia patients. The sponsor has not provided sufficient evidence to support the validity and reliability of these tests to detect subtle cognitive effects that may be the result of treatment in otherwise healthy subjects. Use of these scales is like determining if a drug has no effect on weight using a scale that only detects changes of 25 pounds or more.

In study GGGN, cognitive function was assessed using a series of tests of unclear clinical significance in a relatively small number of subjects. Affect was assessed using a questionnaire. Of the 50 or more comparisons made, there were differences found in the analysis of the 143 subjects that favored the high dose, low dose and placebo groups. Arguments can be made that the drug causes cognitive problems since some "positive" effects seen in the low dose or placebo was not seen with the higher dose. The clinical significance of any one of the changes is not clear.

All of the assessment of cognitive function in healthy subjects were retrospective. We usually do not rely on these post hoc analysis for determining the efficacy of a particular treatment or to definitively state the lack of a specific toxicity. When we don't see a specific adverse event, we usually don't state that the drug does not cause the specific adverse event because it is based on data from a relatively small number of specially selected subjects. On the other hand, we do rely on these types of assessments to raise questions regarding the dangers of a drug in producing a particular adverse event. To evaluate the question, the sponsor should consider a well controlled, adequately designed and powered study to prospectively assess the effect with valid and reliable scales.

/S/
Randy Levin
Neurology Team Leader

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20815 (S-003)**
Sponsor:	**Eli Lilly**
Drug:	**Raloxifene (Evista®)**
Proposed Indication:	**Post-Menopausal Osteoporosis**
Material Submitted:	**Consult from HFD-510**
Correspondence Date:	**4/28/99**
Date Received / Agency:	**5/13/99**
Date Review Completed	**7/16/99**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This review is in response to a consultation request from the Division of Metabolic and Endocrine Drug Products (HFD-510).

Raloxifene (Evista®) is a drug approved in this country for the **prevention** of post-menopausal osteoporosis. It is stated to be a selective estrogen receptor modulator; this group of drugs has been designed with the intention to preserve the beneficial effects of estrogens, such as protection against cardiovascular diseases and osteoporosis, but at the same time have no undesired effects on the reproductive organs. Raloxifene is stated to have an estrogen agonist effect on bone and an antagonist effect on both the breast and uterus. It is not known whether the drug acts as an estrogen receptor agonist or antagonist in the brain.

The sponsor has now submitted a supplemental NDA to the primary reviewing Division (HFD-510) for the use of this drug in the **treatment** of post-menopausal osteoporosis. Both protocols used to support this indication, H3S-MC-GGGK and H3S-MC-GGGN, have included tests of cognitive function in relation to their secondary objectives. Our Division has been requested to review the cognitive function data from these studies.

The cognitive function data made available to us comprises 2 volumes that contain a series of discontinuous excerpts from the original Supplemental NDA. As a result, the organization of the materials in these volumes is less than optimal and the submission somewhat difficult to review.

The section of the draft labeling for raloxifene submitted by the sponsor contains the following statement in regard to cognitive function and affect (in the "Precautions" section):

"*Cognition and Affect*—Evista® has not been associated with deterioration of cognitive function or a change in affect. Any such change during Evista® use is unlikely to be related to therapy, and should be investigated as clinically indicated".

Protocol H3S-MC-GGGK has already been reviewed by me, as a consultation from HFD-510, on 1/27/98.

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2. Summary of Efficacy Studies

The following is a tabular summary of the efficacy studies in this Supplemental NDA

Study #	H3S-MC-GGGK	H3S-MC-GGGN
Design	Randomized, double-blind, placebo-controlled, parallel-arm	Randomized, double-blind, placebo-controlled, parallel-arm
Treatment Arms	Raloxifene 120 mg daily Raloxifene 60 mg daily Placebo	Raloxifene 120 mg daily Raloxifene 60 mg daily Placebo
Duration Of Double-Blind Treatment *	36 months	12 months
Randomized Population (Number of Patients)	Placebo: 2576 Raloxifene 60 mg daily: 2557 Raloxifene 120 mg daily: 2572	Placebo: 48 Raloxifene 60 mg daily: 48 Raloxifene 120 mg daily: 47
Completer Population (Number of Patients)	Placebo: 1924 Raloxifene 60 mg daily: 1972 Raloxifene 120 mg daily: 2005	Placebo: 43 Raloxifene 60 mg daily: 42 Raloxifene 120 mg daily: 40
Main Inclusion Criteria	Osteoporosis-based	Osteoporosis-based
Cognitive and Related Outcome Measures **	• Cognitive and Neuropsychomotor Test Battery • Affective Rating Scale • MAPS Battery	• MAC Psychometric Battery • Affective Rating Scale • Walter Reed Performance Assessment Battery

* The double-blind treatment phase of H3S-MC-GGGK study is ongoing; the 36-month report has been included in this Supplemental NDA. For H3S-MC-GGGN the duration referred to is that of the double-blind, placebo-controlled phase.

** These outcome measures are those listed in the study report; all these measures were not necessarily pre-specified in the protocol

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3. Review of Study # H3S-MC-GGGK

Note that this study is currently ongoing: the 36-month data are presented below.

OUTLINE OF ORIGINAL PROTOCOL

The outline of the original protocol is taken from my earlier review, dated 1/27/98

Title

Comparison of Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women with Osteoporosis.

Objectives

Primary

- To establish the efficacy of long-term treatment with raloxifene, compared with placebo, in the treatment of post-menopausal osteoporosis, as measured by the rate of vertebral fractures and lumbar spine-femoral neck bone mineral density
- To establish the safety of long-term use of raloxifene in the treatment of post-menopausal osteoporosis.

Secondary

- To establish the effect of long-term treatment with raloxifene on the prevalence of Alzheimer's disease in patients with post-menopausal osteoporosis
- To establish the effects of long-term treatment with raloxifene on the prevalence of dementia associated with cerebrovascular disease in patients with post-menopausal osteoporosis
- To establish the effect of long-term treatment with raloxifene on the prevalence of all causes of dementia in patients with post-menopausal osteoporosis
- To assess the possible impact of long-term treatment with raloxifene on cognitive and neuropsychomotor function
- To establish the effect of raloxifene, compared with placebo, on a variety of markers of osteoporosis, other than the above, in patients with post-menopausal osteoporosis
- To establish the effect of raloxifene, compared with placebo, on serum lipids, other laboratory markers of cardiovascular risk, medical resource utilization, quality of life in those with prevalent vertebral fractures, breast and endometrial cancer and risk of cardiovascular disease, in patients with post-menopausal osteoporosis

Design

- A multinational, randomized, double-blind, placebo-controlled, study on post-menopausal women

- The main study will consist of 2 parallel substudies, performed on separate populations. Substudy I will enroll women with a low bone mineral density. Substudy II will enroll women with prevalent vertebral fractures. Patients will be enrolled in Substudies I and II, in an approximate ratio of 2 and 1, respectively.
- All participants will be assigned randomly to one of 3 treatment groups
  Raloxifene 60 mg daily
  Raloxifene 120 mg daily
  Placebo
- The study will consist of the following 4 phases; the screening phase will be inclusive of the single-blind enrollment phase

Screening phase	≤ 40 days
Single-blind enrollment phase during which all patients will be treated with placebo	≤ 28 days
Double-blind core treatment phase	36 months
Double-blind extension phase	12 months

Duration

4 years

Sample Size

6500 patients, in 25 countries, mainly in North America and Europe

Selection

Key Inclusion Criteria

- Ambulatory women, ≤ 80 years, free of severe or chronically disabling medical conditions, life expectancy of at least 5 years, expected to remain ambulatory throughout the study
- Post-menopausal: last menstrual period at least 2 years before beginning study; laboratory confirmation of menopause in women who have had a hysterectomy
- No language barrier, cooperative, expected to return for follow-up visits
- Informed consent
- Criteria for diagnosing osteoporosis as specified in protocol (these differ for each substudy as noted above)

Key Exclusion Criteria

- A variety of skeletal disorders including very severe vertebral disease caused by osteoporosis
- Severe post-menopausal symptoms needing estrogen replacement therapy
- Known or suspected neoplasms that might be estrogen dependent; other forms of cancer within the previous 5 years except for basal cell carcinoma and squamous cell carcinoma of the skin
- Abnormal uterine bleeding
- History of deep vein thrombosis (excluding that due to accidents), other thromboembolic disorders and stroke within the previous 10 years
- A number of hepatic, renal, endocrine and gastrointestinal disorders

- Alcohol or drug abuse
- Poor medical or psychiatric risks for use of an investigational drug
- Use of specified doses of the following drugs, at/for specified periods prior to the study: androgens, estrogens, progestins, calcitonin, systemic corticosteroids, fluorides, biphosphonates and Vitamin D
- Any dose of the following medications at study entry: lithium, anticonvulsants (only if Vitamin D deficient) and phosphate-binding antacids, if used regularly
- Need for high (> 7500 IU daily) doses of heparin for a total period that will exceed 6 months at study entry
- Use of an investigational drug within 28 days prior to study entry
- Participation in any other trial of raloxifene

Concomitant Medications

- None of the above excluded medications should ideally be taken during the study with the following exceptions: other medications for osteoporosis during the 4th year of the study
- Those who begin taking sex hormones and related compounds (other than estriol up to 2 mg daily or intravaginal estrogen upto 3 times per week) must stop the double-blind medication immediately, but may resume their participation in the study once the offending medication is discontinued.

Dosage

- As noted above, during the double-blind phases of the study, the participating subjects will be in 3 treatment groups, to which they were randomized: raloxifene 60 mg daily, raloxifene 120 mg daily and placebo
- Prior to the double-blind phases, all subjects will participate in a single-blind run-in phase during which they will (all) receive placebo
- All study medication will be administered in tablet form
- Beginning from the start of the single-blind enrollment phase, and continuing throughout the remainder of the study. all subjects will receive calcium and Vitamin D supplements, in open-label form, in the following doses

Elemental calcium	Approximately 500 mg per day
Vitamin D	Approximately 400 to 500 IU per day

Schedule

Core Schedule of Visits

- The screening phase will begin on Day minus 40 and extend upto the start of the single-blind enrollment phase
- The single-blind enrollment phase will begin on Day minus 40 and extend upto Day minus 2
- Individual visits will be as follows

Visit	Timing
Visit 1	Enrollment
Visit 2	Week 0
Visit 3	Week 3

Visit 4	Week 6
Visit 5	Week 12
Visit 6	Week 18
Visit 7	Week 24
Visit 8	Week 30
Visit 9	Week 36
Visit 10	Week 42
Visit 11	Week 48

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- Cognitive and neuropsychomotor testing (see below) will be performed at Visits 2, 4, 5, 7, 9 and 11
- The Affective Rating Scale, will be checked at Visits 2, 4, 5, 7, 9 and 11

Scheme for Cognitive (and related)Tests

- All participants in the study will undergo cognitive and neuropsychomotor testing at the times outlined above
- Except at 2 US centers, testing will consist of a Cognitive and Neuropsychomotor Test Battery consisting of the following: Short Blessed Test, Word List Memory, Word Fluency, Trailmaking A, Trailmaking B, Word List Recall, Affective Rating Scale, Static Balance and Gait . The Short Blessed Test is a validated 6-item measure that is used to screen subjects for the presence of global cognitive impairment. The sponsor reports that over 90 % of normal elderly subjects have a Short Blessed Test score ≤ 6. Certain tests are to be omitted at centers in countries where translations of these tests into the local language are unavailable

The entire Test Battery will be used in countries where the main language is English; an abbreviated battery will be used in other countries (the Short Blessed Test will however be common to all countries)

- At 2 US centers, testing will consist of the "MAPS Battery", the full details of which are with a previous submission not immediately available to this reviewer, (but requested from HFD-510). That Battery includes the "Buschke test", presumably the Buschke Selective Reminding Test.

- An algorithm, referred to as the **Dementia Diagnostic Evaluation**, will be used to diagnose dementia in the study population. The following will be the steps in the process

All patients with Short Blessed Test scores ≥ 6 at Week 24 will be entered in the Dementia Diagnostic Evaluation; in addition in each country, approximately 10 – 15 % of patients with the lowest cognitive function based on highest Short Blessed Test scores at Week 24 will be entered in the Dementia Diagnostic Evaluation. So will patients undergoing the MAPS Battery if the average of their consistency scores on trials 2 and 3 of the Buschke test (see uncertainty regarding the nature of this test noted above) at Week 24 is < 0.6. Patients will also be entered in the Dementia Diagnostic Evaluation if the clinical investigator

identifies them as cognitively impaired. Those who are not entered in the Dementia Diagnostic Evaluation will be considered to be cognitively normal.

The Dementia Diagnostic Evaluation will consist of 2 parts.
In **Part 1,** a consulting clinician (assisted, if needed, by designated staff) will interview the patient and caregiver to obtain a full medical history as well as details of cognitive function and functional abilities, obtain a list of current and recent medications, perform a physical and neurological examination, and administer the following rating scales: Mini-Mental Status Examination, Clinical Dementia Rating, Geriatric Depression Scale and Hachinski Ischemic Score. The clinician will then assess whether dementia is present or absent. If the clinical impression is that of dementia and/or the Mini-Mental Status Examination score is < 24, the patient will be referred for Part 2 of the Dementia Diagnostic Evaluation.
In **Part 2,** those patients referred for that section of the evaluation will undergo the following tests: brain CT or MAGNETIC RESONANCE IMAGING without contrast, FTA, Vitamin $_{B12}$, serum folate and TSH. Brain imaging will not be performed if the patient has had a technically adequate study within the preceding 6 months and a copy of the scan is available for review. All scans will be read centrally.
Based on the above Dementia Diagnostic Evaluation, the consulting clinician will determine the patient's cognitive status as belonging to one of the following categories:
Cognitively normal
Mild cognitive impairment
Alzheimer's disease
Dementia associated with cerebrovascular disease
Other type of dementia

- Next, a Dementia Adjudication Committee will review all the above results and again determine which of the above 5 categories, each patient falls into. The Committee will also determine, for each patient who is classified as being demented, whether cognitive impairment preceded the use of study medication.
  The investigator, consulting clinician, central reader of brain imaging studies and Dementia Adjudication Committee will be blinded as to what treatment group each patient belongs to.
- Definitions for each of the above 5 diagnostic categories are in the following table

CATEGORY	DEFINITION
Cognitively normal	No cognitive deficit
Mild cognitive impairment	Cognitive deficit, but no dementia
Alzheimer's disease	NINCDS-ADRDA criteria
Dementia associated with cerebrovascular disease	Objective evidence of dementia; and a clinical history of stroke prior to onset of dementia, with physical signs and symptoms referable to a neuroanatomically distinct cortical lesion, or clear radiographic evidence of infarction in a defined vascular territory
Other type of dementia	Dementia without satisfying criteria for Alzheimer's disease or dementia associated with cerebrovascular disease

- The sponsor also states that the algorithm referred to above will be employed to diagnose and classify dementia in patients belonging to the entire cohort, **after Visit 7 and until the end of the trial**

Other assessments

- Measures of efficacy will include clinical, biochemical and radiological markers of osteoporosis, biochemical markers of cardiovascular risk, clinical assessments of cardiovascular disease, and measures of resource utilization and quality of life; the details and timing of these assessments are in the protocol
- Measures of safety will include vital signs, gynecological examinations, pelvic ultrasound, mammography, electrocardiograms, and routine hematology, chemistry and urinalysis at predefined timepoints during the study
- Pharmacokinetic measures will consist of estimating study drug plasma levels of a subset of patients at specific timepoints during the study

Outcome Measures

Primary

For each patient the primary outcome variable will be the prevalence of Alzheimer's disease, as defined by the Dementia Adjudication Committee. The prevalence of Alzheimer's disease for each treatment group will thus be calculated

Secondary

Prevalence of dementia due to cerebrovascular disease, and dementia due to all causes, in each treatment group (these categories of dementia are as defined by the Dementia Adjudication Committee)

Safety Monitoring

The measures used are as listed above

Analysis Plan

- The following discussion pertains to the analysis of the cognitive assessments alone
- All treatment comparisons will be by intention-to-treat, between raloxifene and placebo, or between treatment arms

Primary Efficacy Parameter

- As noted above for each patient the primary outcome variable will be the diagnosis of Alzheimer's disease, the prevalence of Alzheimer's disease in each treatment group will thus be calculated. To relate the risk of Alzheimer's disease with the other potential risk factors, generalized linear modeling techniques will be used
- Using the above techniques, the relative risk of Alzheimer's disease for each raloxifene group compared with placebo will be computed, controlling for known extraneous sources of variation, such as country of origin. The results

of this analysis will be presented in terms of relative risks and 95 % confidence intervals of the relative risks

- As an additional analysis the prevalence of Alzheimer's disease will be assessed using a chi-square test statistic on the proportion of patients with Alzheimer's disease in each treatment group; dose-response trends will be analyzed using a gamma statistic.
- Similar analyses of the prevalence of Alzheimer's disease will be performed after removing the patients with evidence of pre-existing dementia, as defined by the Dementia Adjudication Committee

Secondary Efficacy Parameters

The effect of raloxifene on the prevalence of dementia due to cerebrovascular disease, and on the prevalence of all causes of dementia will be determined using the categorical analyses methods described above

The sponsor also states that "additional exploratory analyses of the data not described here will be considered as deemed appropriate and statistical methods described here may change based on advances in research"

Safety Parameters

These have already been outlined above

Sample Size Rationale

- A previous prospective study, cited by the sponsor, has shown that the annual incidence of Alzheimer's disease in a population similar to that in this trial is approximately 1.5 %. The sponsor believes that the because of study exclusion criteria, only a negligible number of patients in this study are likely to have Alzheimer's disease at enrollment. Thus, the predicted prevalence of Alzheimer's disease in the study population at the end of 3 years is approximately 4.5 %.
- Drop-out rates were estimated on the basis of a blinded examination of the available baseline Short Blessed Test scores of the patients who have dropped out in the first year of the study. On this basis, drop-out rates of 12.6 % per year for patients with cognitive impairment, and 9.7 % per year for those without cognitive impairment are assumed
- A large prospective study, cited by the sponsor, has indicated that the relative risk of developing Alzheimer's disease in estrogen users is 0.69 relative to non-users. Assuming a relative risk of 0.6 for raloxifene- compared with placebo-treated patients, and a sample size of 2463 patients per treatment arm, the power will 79 % to detect a difference ($\alpha = 0.05$), and 93 % to detect a trend ($\alpha = 0.20$) in the prevalence of Alzheimer's disease after 3 years of study. Pooling the 2 raloxifene groups increases the power to 87 % to detect a difference and 96 % to detect a trend at the above levels of significance.
- Because of limited information on the protective effect of estrogen on dementia associated with cerebrovascular disease and other types of dementia no power calculation has been made for these entities