NDA SUPP AMEND SE1-003-BL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

June 11, 1999

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

NDA AMENDMENT

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

Reference is made to the submission (March 30, 1999) of a supplemental NDA (sNDA, S-003) for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

In the referenced sNDA submission, a draft of proposed changes to the patient package insert was provided. As discussed in a phone conversation (February 3, 1999) between Dr. Paul Gesellchen (Lilly) and Mr. Randy Hedin (FDA), Lilly has received a number of negative comments on the readability of the current patient package insert since the launch of Evista in January of 1998. To address some of the consumer and physician concerns about the patient package insert Lilly has employed a consultant (Dorothy Smith, PharmD, President, Consumer Health Information Corporation) to assist in rewriting the insert with a focus on simplification of the language.

We are herewith submitting a revised draft patient package insert based on input from this consultant. This version of the draft patient package insert is meant to supercede the version that was submitted to the Agency (March 30, 1999) as part of the sNDA. For ease of review, all deletions from the current patient package insert or moves to new sections have been denoted by strikethroughs in large (18 point) font, while all additions have been denoted by large (18 point) font. Words and sections that remain the same remain the same as in the currently approved insert are in normal (12 point) font. In addition, as discussed between Mr. Hedin and Dr. Gesellchen, annotations have been added to the right hand margin of most pages in order to assist the reviewer in understanding the reasons for the proposed changes or movements of any sections.

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

Sincerely,

ELI LILLY AND COMPANY

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

Enclosures

cc: Mr. Randy Hedin (5 desk copies)

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

June 11, 1999

Noted
GK
7/7/99

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

NDA AMENDMENT

NDA SUPP AMEND
SE1-003
BH

6/11/99

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

Reference is made to the submission (March 30, 1999) of a supplemental NDA for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

SRM
6-18-99

Reference is made to a phone conversation (May 27, 1999) between Eric Colman, MD (FDA) and Paul Gesellchen, PhD (Lilly). In this conversation, Dr. Colman referred to the recent submission (May 25, 1999) of responses to questions that he had asked on May 11, 1999. Dr. Colman asked one follow-up question.

We are herewith providing written responses to this question (Attachment).

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

Sincerely,

ELI LILLY AND COMPANY

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

REVIEWS COMPLETED
CSO
LE
MEMO
CSO
DATE

Enclosures

cc: Dr. Eric Colman (desk copy)
Mr. Randy Hedin (cover letter only)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

May 25, 1999

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

NDA AMENDMENT

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

Reference is made to the submission (March 30, 1999) of a supplemental NDA for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

Reference is made to a Fax transmission received (May 11, 1999) by Dr. Paul Gesellchen from Mr. Randy Hedin. This Fax contained nine separate medical questions concerning the supplemental NDA.

We are herewith providing written responses to these nine questions (Attachment).

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

Sincerely,

ELI LILLY AND COMPANY

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

Enclosures

cc: Mr. Randy Hedin (cover letter only)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

May 20, 1999

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

NDA AMENDMENT

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

Reference is made to an e-mail communication (May 5, 1999) from Eric Colman, MD to Paul Gesellchen, PhD. In this communication, Dr. Colman requested that Lilly provide the FDA with further information related to the adverse event of diabetes. Reference is also made to a phone conversation (May 6, 1999) between Dr. Gesellchen and Dr. Colman in which Dr. Gesellchen clarified what type of information Lilly would be able to provide regarding diabetes.

We are herewith providing the requested information (Attachments).

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

Sincerely,

ELI LILLY AND COMPANY

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

Enclosures

cc: Mr. Randy Hedin (cover letter only)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

May 20, 1999

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

GENERAL CORRESPONDENCE

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

Reference is made to the submission (March 30, 1999) of a supplemental NDA (sNDA) for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

Reference is also made a meeting (April 23, 1999) between Dr. David Hoberman (FDA) and Dr. Paul Gesellchen (Lilly). In that conversation, Dr. Hoberman stated that he will request that Lilly provide him with specific variables from our recent sNDA submission merged into one SAS dataset for ease of his review. Please also refer to an e-mail request (May 6, 1999) from Dr. Hoberman which was forwarded to Dr. Gesellchen via Mr. Randy Hedin (FDA) in which the required dataset variables were specified. Finally, reference is made to a phone conversation (May 7, 1999) between Dr. Hoberman and Dr. Ronald Knickerbocker (Lilly) during which details of the Agency request were clarified and finalized.

We are herewith providing the requested dataset in 3.5 inch diskette format per Dr. Hoberman's request. The attachment contains a description of the data that is contained on this diskette as well as some technical comments about the data.

The electronic media was checked by Lilly personnel and has been verified to be free of known viruses. The virus checking software was McAfee v4.02 using Virus Definitions 4.0.4025 created on 6-May-1999.

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

Sincerely,

ELILLILLY AND COMPANY

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

Enclosures

cc: Mr. Randy Hedin (cover letter only)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

April 28, 1999

GENERAL CORRESPONDENCE

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

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

Reference is made to the submission (March 30, 1999) of a supplemental NDA for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

Reference is also made to a phone conversation (April 21, 1999) between Mr. Randy Hedin (FDA) and Dr. Paul Gesellchen (Lilly). In that conversation, Mr. Hedin requested a desk copy of all summary documents from the sNDA submission that pertained to cognitive function. This request was begin made to allow for a consult with the FDA Division of Neuorpharmacological Drug Products regarding the cognitive function data contained within the sNDA.

We are herewith providing the requested documents in two volumes. These documents include protocols H3S-MC-GGGK(f), and H3S-MC-GGGN(a), and cognitive function-related sections from the final study reports for both protocols, from the Integrated Summary of Safety, the Integrated Summary of Effectiveness, and the Application Summary. All of the enclosed documents are exact copies of the documents that were provided as part of the initial sNDA submission. No new data is being provided. At the request of Mr. Hedin, only this cover letter is being submitted to the NDA file. The actual documents are being delivered as a desk copy to Dr. Eric Colman under separate cover.

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

Sincerely,

ELI LILLY AND COMPANY

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

Enclosures

cc: Mr. Randy Hedin (cover letter only)
Dr. Eric Colman (cover letter and documents)

SE1-003 BS

ORIGINAL

NDA SUPPL AMEND

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

April 27, 1999

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

NDA AMENDMENT

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

Reference is made to a conversation (April 23, 1999) between Dr. David Hoberman (FDA) and Dr. Paul Gesellchen (Lilly) regarding the statistical review of the supplemental NDA for the referenced drug product (submitted on March 30,1999). In that conversation, Dr. Hoberman requested a printout of the PROC contents for the datasets that were used to perform the statistical analyses for the primary clinical study (H3S-MC-GGGK) from the supplemental NDA.

We are herewith providing the requested PROC contents tables for the 13 datasets from the submission.

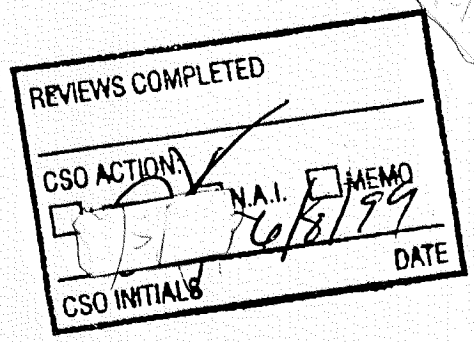
Please call either the lead statistician for the GGGK protocol, Dr. Ronald K. Knickerbocker at (317) 277-2242, the U.S. regulatory affairs contact, Dr. Paul D. Gesellchen at (317) 276-4306, or me at (317) 276-4038 if you require any additional information or if there are any questions.

Sincerely,

5/4/99

ELI LILLY AND COMPANY

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



Enclosures

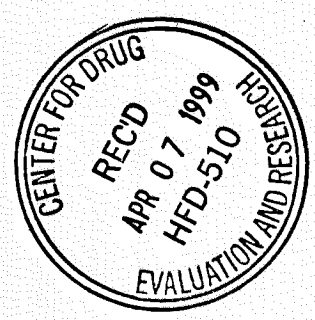
cc: Mr. Randy Hedin, cover letter only
Dr. David Hoberman, desk copy

6-1-99

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

April 6, 1999



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: **Mr. Randy Hedin**
5600 Fishers Lane
Rockville, MD 20857-1706

RE: DELIVER DIRECTLY TO MR. RANDY HEDIN

Reference is made to a phone conversation (March 19, 1999) between Mr. Randy Hedin (FDA) and Dr. Paul Gesellchen (Lilly). In that conversation Mr. Hedin requested that Lilly provide the FDA with a specific set of duplicate documents from the impending supplemental NDA 20-815 for raloxifene hydrochloride (Evista®) for the treatment of osteoporosis in postmenopausal women. These documents are required for inclusion in the Action Package.

We herewith submit the requested documents as outlined below. We certify that these documents are identical to those documents that were submitted with our supplemental NDA submission (March 30, 1999). For convenience, the first six documents have been packaged together in one volume and they are separated by identifying tabs.

	Document	**Size**
1.	sNDA cover letter	5 pages
2.	The 356h form	2 pages
3.	Patent/Exclusivity statements	1 page
4.	Debarment statement	1 page
5.	Draft physician package insert (non-annotated)	31 pages
6.	Draft patient package insert (non-annotated)	7 pages
7.	Integrated summary of efficacy	1 volume
8.	Integrated summary of safety	2 volumes plus 2 volumes of appendices

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

Sincerely,

ELI LILLY AND COMPANY

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

Enclosures

March 30, 1999

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

SUPPLEMENT
Expedited Review Requested

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

Reference is made to the approval (December 9, 1997) of EVISTA® (raloxifene hydrochloride) for the prevention of osteoporosis in postmenopausal women. This letter accompanies a submission by Eli Lilly and Company (Lilly) of a supplemental New Drug Application (sNDA) for EVISTA for the new indication of the treatment of osteoporosis in postmenopausal women. The archival version of this submission contains 196 paper volumes and 2 CD-ROMs. Items 11 and 12 (Case Report Tabulations and Case Report Forms) are provided as electronic archival copies on the CD-ROMs.

The primary conclusions concerning the safety and efficacy of EVISTA are based on the 36-month analysis of data from 7705 randomized subjects in a large Phase 3 osteoporosis treatment trial (Study H3S-MC-GGGK) utilizing vertebral fracture rates along with lumbar spine and femoral neck bone mineral density as primary efficacy endpoints. Supportive information from two smaller Phase 2 clinical trials (H3S-MC-GGGN and H3S-MC-GGGP) and from a pharmacokinetic clinical trial (H3S-MS-GGIP) are also provided.

Lilly believes that the sNDA for EVISTA warrants an expedited review. The rationale for this conclusion is described in the Note to Reviewers that is located in this first volume [1:3.1 p12]. Certain pagination and naming conventions that are used in this sNDA along with a table which identifies the location of critical review documents are also described in the Note to Reviewers section.

Lilly has met with FDA personnel on a number of occasions to discuss the development program for EVISTA since filing the IND for this drug (IND [redacted] on April 26, 1992. The interactions and agreements from those meeting are outlined in the Application Summary, H.2.1.3. Regulatory History and Agreements [3:3.1 p135].

Reference is made to the agreement between the Agency and Lilly with respect to the electronic format of the archival version of Item 11 (Case Report Tabulations). This agreement to use the Adobe Portable Document format for the archival copy of Item 11 was documented in a General Correspondence submission (February 16, 1999) to the referenced NDA file. With this exception and those noted in the sNDA Briefing Document that was submitted (July 31, 1998) to the NDA file as General Correspondence, this application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" and the ""Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications".

An electronic version of the complete sNDA is also provided in Adobe Portable Document Format on CD-ROM media as a reviewer aid. This electronic review copy represents a complete and identical electronic copy of all 196 paper volumes that are being submitted as part of this application and includes the complete set of Case Report Tabulations (Item 11) and Case Report Forms (Item 12). All volume and page numbers in the electronic review copy match the volume and page numbers in the paper volumes. Please note that the first CD-ROM disk contains a README.PDF file. This file describes the content and format of this electronic review copy of the sNDA. The CD-ROMs are located in a separate binder marked "Review Aids – Not for Archive" located with the paper review copy for Item 1 and are intended for installation on the FDA local area network. This installation will allow all reviewers (e.g., biopharmaceutics, biometrics, and medical) to access the full sNDA at their own private workstations. Separate arrangements are being made to instruct the lead reviewers and the senior regulatory management officer in the organization and use of this electronic review copy.

As communicated in a phone call (March 17, 1999) from Dr. Knickerbocker (Lilly) to Dr. Todd Sahlroot (FDA), copies of the SAS datasets, programs, and macros that can be used to recreate the main safety and efficacy analyses for the large osteoporosis treatment study, H3S-MC-GGGK, are also provided on CD-ROM media as a reviewer aid. This single CD-ROM is located in a separate binder marked "Review Aids – Not for Archive" located with the paper review copy for Item 10 (Statistical Section).

As described in the sNDA Briefing Document (July 31, 1998), this submission is also accompanied by electronic media (five CD-ROMs) which contain pharmacokinetic and pharmacodynamic datasets and key output files that were generated during the detailed pharmacokinetic analyses of the raloxifene data. As with the previous raloxifene NDA submission, FDA requested, specifically formatted summaries of the human pharmacokinetic studies are provided for the biopharmaceutical reviewer. These summaries may be found both in the pharmacokinetic section [6:3.1 p53] as well as with the final clinical reports [8:3.7 p51]. The five UNIX-based CD-ROMs are located in a separate binder marked "Review Aids – Not for Archive" located with the paper review copy for Item 6 (Human Pharmacokinetics and Bioavailability Section).

All electronic media have been checked by Lilly Information Technology personnel and have been verified to be free of known viruses. The virus checking software was McAfee v3.2.0 using Virus Definitions 3.0.3202 created on 15-Feb-1999.

The User Fee of for this submission has been paid under User Fee number A check for this amount was sent to Mellon Bank on March 25, 1999 by Federal Express overnight mail. Form 3397 has been provided.

A Debarment Certification has been provided.

Reference is made to the agreement between the Agency and Lilly with respect to the reporting of financial information for investigators who participated in the pivotal efficacy trials. This agreement was documented in a General Correspondence submission (January 18, 1999) to the referenced NDA file. Form 3454 has been provided.

To co-ordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications, concerning this file, regardless of subject, be directed to:

Gregory G. Enas, Ph.D.
Director
U. S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number: (317) 276-1652

Telephone calls should be made between the hours of 7:30 a.m. and 4:15. p.m. (EST). Any calls regarding this submission should be made to:

Paul D. Gesellchen, Ph.D.
(317) 276-4306 (work)
(317) 578-3816 (home)
(800) 356-1643 (alphanumeric pager)

or alternatively you may reach Dr. Gesellchen via E-mail at pdg@lilly.com.

In the case of Dr. Gesellchen's absence please contact:

Gregory G. Enas, Ph.D.
(317) 276-4038 (work)
(317) 328-9213 (home)

On holidays, Saturdays, or Sundays, call Dr. Gesellchen or Dr. Enas at home using the telephone numbers indicated.

Any calls relating to functionality of the electronic portion of the submission should be made to:

Steven T. Ward
(317) 276-2952 (work)
(317) 879-8825 (home)
(317) 256-8888 (digital pager)

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

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

Sincerely,

ELI LILLY AND COMPANY

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