

Lilly

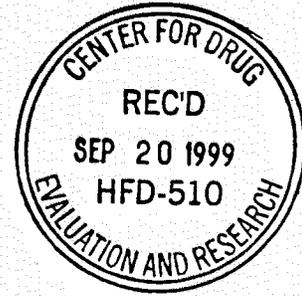
Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

NDA SUPP AMEND

SEI-003/62

DUPLICATE



September 17, 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), S-003

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 submission (August 24, 1999) of an sNDA amendment with responses to FDA questions regarding breast cancer adjudication data. Please also refer to a Fax communication (September 15, 1999) from Mr. Alvis Dunson (FDA) to Dr. Paul Gesellchen (Lilly). This communication contained three questions relating to breast cancer data in the referenced sNDA submission.

We are herewith providing the FDA with responses to the three questions and a revised "marked-up" version of the Effects on the Breast subsection of the CLINICAL PHARMACOLOGY section of draft physician package insert (Attachment). Please note that new changes to the package insert have been highlighted in a pink color in the electronic version which prints in gray on a black and white printer. This version of the draft package insert will supersede all previous versions.

Food and Drug Administration
NDA, 20-815 (S-003), EVISTA®
September 17, 1999
Page 2

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



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

Enclosures

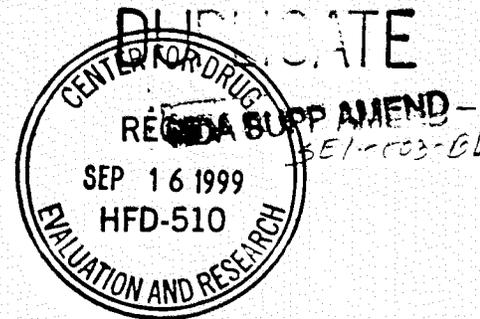
cc: Mr. Randy Hedin (HFD-510, cover letter only; plus 1 encrypted E-mail copy and one Faxed copy of Attachments B and C)
Mr. Alvis Dunson (HFD-150, two desk copies)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

September 15, 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), S-003

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 an encrypted E-mail transmission (September 10, 1999) from Mr. Randy Hedin (FDA) to Dr. Paul Gesellchen (Lilly). This communication contained FDA-proposed changes to the draft package insert.

We are herewith providing the FDA with a revised "marked-up" version of the draft physician package insert (Attachment) which contains the Lilly responses to the changes that were requested in the referenced E-mail communication. As agreed to in a phone conversation (September 15, 1999) between Mr. Hedin and Dr. Gesellchen, we have not responded to FDA comments in the Drug-Drug Interactions section, but will do so once we have received package insert comments from the Biopharmaceutics Reviewer.

We have utilized the package insert version that was submitted to us on September 10, 1999. We have modified that document by adding our responses to the FDA comments and proposed changes to the boxes to the right of the affected label text. Additionally, where we are suggesting alternate wording we have made those changes in the body of the package insert and highlighted these changes in a pink color, to be differentiated from the yellow highlighted changes provided by the FDA reviewer [Note that these two colors will print in different shades of gray on a black and white printer, thus making it possible to differentiate the changes.]

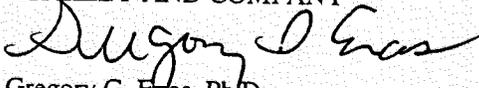
Additionally, in a separate mailing, Lilly will provide a "clean" copy of the draft package insert in which all modifications have been incorporated. This version of the draft package insert will supersede all previous versions.

Food and Drug Administration
NDA. 20-815 (S-003), EVISTA®
September 15, 1999
Page 2

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. Elias, Ph.D.
Director
U. S. Regulatory Affairs

Enclosures

cc: Mr. Randy Hedin (cover letter only and 1 encrypted E-mail copy)

DUPLICATE
Lilly

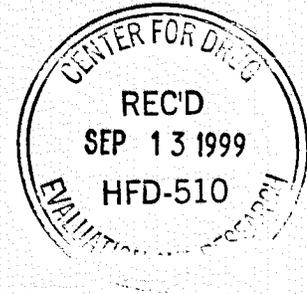
SUPPL NEW CORRESP

SNC

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

September 10, 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.

After submission of the sNDA, several errors were identified in final published documents. These errors were infrequent and do not affect the statistical significance of the analyses or conclusions. For completeness sake, we are providing the reviewers with summaries of the errata and the specific portions of documents (text, tables, and figures) that were affected. To assist the reviewers, all deletions to the document have been identified by ~~striketroughs~~, while all additions have been identified by the use of the underscore.

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

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

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

Enclosures

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

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

August 26, 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.

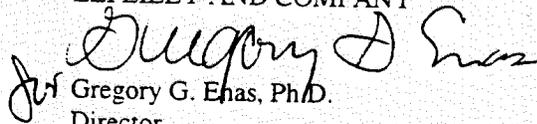
Reference is also made to an E-mail communication received (August 11, 1999) by Dr. Paul Gesellchen from Dr. Eric Colman. This communication contained four questions from the FDA Division of Reproductive and Urologic Drug Products concerning the supplemental NDA.

We are herewith providing written responses to those 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


Gregory G. Ehas, Ph.D.
Director

U. S. Regulatory Affairs

Enclosures

cc: Mr. Randy Hedin (cover letter only plus 2 desk copies)



Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

August 24, 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 also made to an E-mail communication received (August 6, 1999) by Dr. Paul Gesellchen from Mr. Randy Hedin. This communication contained one question from the FDA Oncology Medical Reviewer concerning the supplemental NDA.

We are herewith providing written responses to that 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

Gregory G. Enas, Ph.D.

Director

U. S. Regulatory Affairs

Enclosures

cc: Mr. Randy Hedin (cover letter only plus 2 desk copies)
Mr. Alvis Dunson, HFD-150 (desk copy)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

August 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)

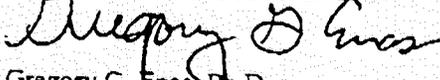
Reference is made to the submission (March 30, 1999) of a supplemental NDA for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

Reference is also made to the submission (May 25, 1999) of responses to a medical questions including one question regarding weight gain observed in some patients in the osteoporosis treatment trial. Please also refer to the submission (August 9, 1999) of a follow-up document concerning the body weight question. We are herewith providing additional commentary relevant to the original 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

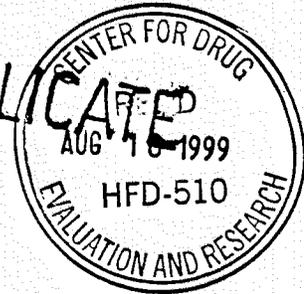
Enclosures

cc: Dr. Eric Colman (desk copy via Fax)
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



August 9, 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

SUPPL NEW ~~COPIES~~ *Amend*

NDA AMENDMENT *SNE*

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

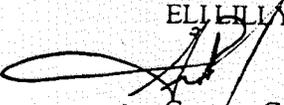
Reference is made to the submission (March 30, 1999) of a supplemental NDA for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

Reference is also made to the submission (May 25, 1999) of responses to a medical questions including one question regarding weight gain observed in some patients in the osteoporosis treatment trial. We have completed additional analyses relevant to that question. We are herewith providing you with an update to the weight-gain 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

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

Enclosures

cc: Dr. Eric Colman (desk copy via Fax)
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

August 6, 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 also made to an E-mail communication (August 3, 1999) from Randy Hedin (FDA) to Paul Gesellchen, PhD (Lilly). In this communication, Mr. Hedin attached a question from the Biopharmaceutics Reviewer.

We are herewith providing a response 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

A handwritten signature in cursive script, appearing to read "Gregory G. Elias".

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

Enclosures

cc: Dr. Ronald Kavanagh (desk copy)
Mr. Randy Hedin (cover letter only)

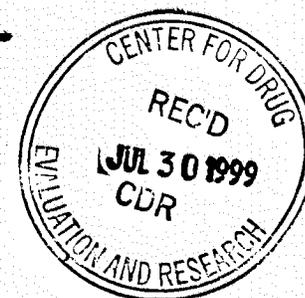
Lilly

Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

July 29, 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

4-MONTH SAFETY UPDATE

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

Reference is made to a supplemental new drug application (NDA 20-815, S-003) submitted on March 30, 1999 for EVISTA® (raloxifene hydrochloride) for the new indication of the treatment of osteoporosis in postmenopausal women.

We are herewith submitting the 4-Month Safety Update (Item 9) for the referenced sNDA. This safety update is comprised of the 4-Month Safety Update Report (one volume) which is supplied in paper format and an archival copy of the case report forms (equivalent to 16 volumes) which is being supplied in electronic format (one CD ROM disk).

The CD-ROM disk contains a README.PDF file. This file describes the content and format of the electronic portion of the submission and contains information on installation procedures.

The CD-ROM disk in this submission has been checked by Lilly Information Technology personnel and has been verified to be free of known viruses. The virus checking software was McAfee v4.0.2 using Virus Definitions 4.0.4025 created on 6-May-1999.

Please call Mr. Steven T. Ward at (317) 276-2952, Dr. Paul D. Gesellchen at (317) 276-4306, or me at (317) 276-4038 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas

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

Enclosures

cc: Mr. Randy Hedin, HFD-510, (Desk copy, cover letter only)
Dr. Eric Colman, HFD-510, (Desk copy, cover letter only)

Randy Hedin

Lilly

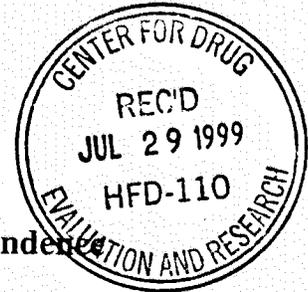
Lilly Research Laboratories

A Division of Eli Lilly and Company

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

July 23, 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 (June 27, 1997) of a summary document entitled "Clinical Relevance of the Ovarian Tumors Observed in Mice Treated with Raloxifene Hydrochloride" as an amendment to the referenced NDA file. We are herewith submitting a revision to the referenced document. Several clarifications have been made to that original document in order to reduce any potential for misinterpretation of the comments in that document. The first page of the enclosed document specifies those changes in detail. Please note that these changes do not affect the Conclusions section of the document.

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

A handwritten signature in cursive script, appearing to read "Gregory G. Enas".

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

cc: Mr. Randy Hedin (desk copy)

DUPLICATE

Lilly

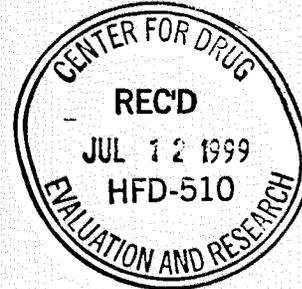
NDA SUPP AMEND
SEI-003
BH

Lilly Research Laboratories

A Division of Eli Lilly and Company

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

July 9, 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 phone conversation and e-mail transmissions (June 11, 1999) from Eric Colman, MD (FDA) to Paul Gesellchen, PhD (Lilly). In these communications, Dr. Colman asked one question regarding BMD effects in lumbar spine of placebo from Study H3S-MC-GGGK.

We are herewith providing written response 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

Michael D. Casper, MD
for Gregory G. Enas, PhD
Gregory G. Enas, Ph.D.

Director

U. S. Regulatory Affairs

Enclosures

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

BEST POSSIBLE COPY

July 8, 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 (S-003) for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women. Please also refer to an E-mail communication received (June 10, 1999) by Dr. Paul Gesellchen from Mr. Randy Hedin. This communication contained five separate questions from the FDA Biopharm reviewer concerning the supplemental NDA. Reference is also made to the submission (June 24, 1999) of an NDA amendment which contained the response to one of the five questions.

We are herewith providing written responses to the remaining four questions (Questions #1-3 and #5, Attachment). This completes the response to the questions received on June 10, 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,

ELI LILLY AND COMPANY

*Michael J. Chapman, MD
for Gregory G. Enas, Ph.D.*

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

Enclosures

cc: Mr. Randy Hedin (cover letter only)
Dr. Ronald Kavanagh (desk copy)

Lilly

Lilly Research Laboratories

A Division of Eli Lilly and Company

June 24, 1999

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

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 (S-003) for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

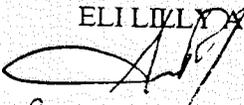
Reference is also made to an E-mail communication received (June 10, 1999) by Dr. Paul Gesellchen from Mr. Randy Hedin. This communication contained five separate questions from the FDA Biopharm reviewer concerning the supplemental NDA.

We are herewith providing written responses to one of those five questions (Question #4, Attachment). The responses to the remaining four questions are forthcoming.

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


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

Enclosures

cc: Mr. Randy Hedin (cover letter only)
Dr. Ronald Kavanagh (desk copy)