Pt. #	Bleeding	RX	HRT	Proc	Path	Sono notes
003-3651	Yes	60	Yes E/P	Asp/poly pectomy	Hyperplastic polyp	
006-0126	Yes	60	No	Asp	Atrophic polyp	
032-2821	Yes	60	No	DC	Hyperplastic polyp	
032-2878	Yes	60	No	DC	Atrophic polyp	
041-3955		120	No	hsc	Polyp, na	1=? 9=8mm
044-5027		60	Yes E	DC	No path record	SIS polyp 1=10mm
044-5083	No	Placebo	No	hsc	Polyp, a	C5 1=2.7 5=14
047-6668	Yes	120	Yes E	Hyst	Functional polyp	
052-8451	Yes	60	No	Emb	Polyp	
055-0460		60	No	Hsc	Polyp ,na	1=5.5mm 5=6.9
055-0479		120		Hsc at 9	Polyp ,na	1=10.2
055-0637		120		Hsc at 6	Polyp ,na	1=6.5 5=8.8
055-0730	No	120			Polyp ,a And ,na ?	C5 1=2.6 5=9
058-5381		120	Yes E/P	Hsc at 5	Polyp ,a	1=7 5=11
058-5394		60		hsc	polyp ,na	1=1 5=8
058-5482		60		asp	polyp	1=4.8 5=5.1
063-4562	Yes	120	No	Asp	Atrophic polyp	
063-4593	Yes	Placebo	Yes E/P	DC	Hyperplastic polyp	
064-4894	No	60			Polyp	C5 1= 4.3 5=13
064-4899		120			5= inad no hsc confirm	1=4.8 5=9 7=14 SIS polyp
068-6939	Yes	120	Yes P	Asp	Polyp	
068-6995	Yes	60	No	Asp	Functional polyp	
071-0109		60		hsc	polyp na	1=4 7=8
071-0134	Yes	120	No	Asp	Atrophic polyp	

071-0230	No	120		hsc	Polyp ,a	C5 1=3 7=14
071-0283	Yes	120	Yes E/P	DC	Polyp fragments	C5
071-0291	Yes	60	No	No bx	none	SIS polyp
071-0492	Yes	60	No	Hsc	Atrophic polyp	
071-0631	Yes	120	No	Asp	Functional polyp	
071-0811	Yes	Placebo	No	Asp	Functional polyp	C5
073-3458		Placebo			Polyp probable	1=4.6 7=6
073-3919		60		DC	Polyp	1=10
077-3003	No	120			Polyp ? Not recorded on Primary dx	C5 1=3 9=9 sis polyp
077-3058		Placebo			Polyp ,a	1=8.7 7=13
077-3082		60			Polyp ,a	1=3.8 5=5.4 7=7
077-4054		60		Hsc	Polyp ,na	1=3.5 5=6.5
077-4181	Yes	60	No	Polypectomy	Functional polyp	
080-5049		Placebo	Yes E		Polyp hyperplasia	9=9
080-5058	Yes	60	Yes E/P	DC	Hyperplastic polyp	
092-5406		120		Hsc	Polyp ,a	1=7 5=9
092-5412		60		Hsc	Polyp ,na	1=5 7=6.8
092-5484		60		Hsc	Polyp ,a	1=9
092-5513	No	120		hsc	Polyp ,na	C5 1=5 5=12
145-3202		120		DC	polyp	1=? 5=7
207-4048		60		Hsc	polyp	1=2 9=5.5
243-0034		Placebo			No path	1=10
243-0135		Placebo		Hsc	Polyp ,na	1=9
243-0156		60			No path	1=7
243-0203		Placebo		Hsc	polyp	1=5 5=8.3
243-0229		120		asp	Atrophic endom	1=?

						5=6? Sis polyp
243-0240	Yes	60	No	Asp	Atrophic polyp	
243-0246		60		Hsc	Polyp ,na	1=5 5=6.1
282-0437		Placebo		Hsc	Polyp ,a	1=6
282-0571	Yes	60	No	Asp	Atrophic polyp	
282-0907	Yes	60	No	No bx	none	SIS polyp
282-0959	Yes	120	Yes E	Asp	Atrophic polyp	
282-0975		60		hsc	Polyp ,a	1=1.8 7=9.4
282-1092		Placebo		Hsc	Polyp ,a	1=21 5=11
742-0334	Yes	120	Yes E	Polypect omy	Polyp	
742-0379	No	60	Yes E	Asp hsc	Polyp ,na	C5 1=1 5=4 7=7
742-3908		120			Atrophic endom	1=1 5=9
742-3930	No	60			Polyp	C5 1=1 5=10
742-3953	No	120	Yes E	asp	Polyp	C5 1=1 5=7
742-4140		120	Yes E	pipelle	Bx not recorded	1=? 5=6
742-4236		60		DC	? bx results	1=? 5=8
742-4258		Placebo		asp	polyp	5=3 9=6
742-4719		Placebo	Yes E	Asp DC	hyperplasia	1=15
804-7559		60				1=6
804-7573	No	60		hsc	Polyp ,a	C5 1=2 5=14
805-6633		Placebo		Hsc	Polyp ,a	1=? 5=12
805-6647	Yes	60	No	DC	Simple polyp	
866-8732	Yes	120	Yes E/P	Poypecto my	Cystic atrophy no polyp listed	
969-2474		Placebo	Yes E	Hsc	Polyp ,a	9=12

Polyps separated by evidence:

Polyps confirmed by pathology where sonography indicated an increase in endometrial thickness, initial sono thickness was =/< than 5mm, and no additional hormones were taken. (4 placebo, 12 taking 60mg, 3 taking 120mg)

Polyps confirmed by pathology where the first sonogram performed showed an increased endometrial thickness of greater than 5mm and no additional hormones were taken. In this case it is hard to say if the polyp was pre-existing. (5 placebo, 2 taking 60mg, 5 taking 120)

Polyps confirmed by pathology in cases were additional hormones were taken.
(3 placebo, 3 taking 60mg, 7 taking 120mg)

Polyps confirmed by pathology where no sonography information is available and no additional hormones taken. Thus we do not know if polyp was pre-existing. (1 placebo, 10 taking 60mg, 2 taking 120mg)

Polyps suspected by sonography but no pathology confirmation, no additional hormones. Here it would be dependent on the skill of the sonographer (0 placebo, 2 taking 60 mg, 3 taking 120 mg)

APPEARS THIS WAY
ON ORIGINAL

Consultation:

HFD-580 review of Evista and uterine polyps for HFD-510

Review of submitted material (Lilly's Raloxifene LY139481 section 7.3.2 Uterine Corpus, pages 163-202)

Summary points of sponsor information:

Genital tract bleeding was initially evaluated according to investigator discretion and later by a set algorithm incorporating transvaginal ultrasound, saline-infusion sonohysterography, and biopsy procedures.

A subset of patients (2155 out of 5957) had annual transvaginal ultrasounds to assess endometrial thickness. Endometrial thickness > 5.0 mm required additional evaluation according to a set algorithm. Trained personnel designated by the investigator performed the ultrasounds. The sponsor reported that the level of detail and recorded information from the ultrasound varied in assessments of the same patient and between study sites.

Approximately 10% of the patients in the study reported concomitant use of estrogens or tamoxifen.

Endometrial and cervical polyps were reported more frequently in the women taking raloxifene compared to the placebo-treated women. The finding of endometrial polyps was statistically significant in the women with bleeding, but not in the group of patients with endometrial thickness greater than 5.0mm.

The statistically significant finding of increased cervical polyps was derived from a pooled comparison of both treatment dosages versus placebo; however, it is noted that this data comes from a table that includes study patients who had a hysterectomy.

Tables emphasizing the histological features of the endometrial polyps in the 25 women with bleeding are included below. The information for these tables is derived from a sponsor submitted table previously requested by HFD- 510.

Atrophic polyps or atrophic endometrium

Pt. #	Rx group	HRT/TAM use	Pathology site/ procedure
006-0126	RLX060	None	Central/pipelle
032-2878	RLX060	None	Central/d&c
063-4562	RLX120	None	Central/pipelle
071-0134	RLX120	None	Central/pipelle
071-0492	RLX060	None	Central/hystero bx & d&c
243-0240	RLX060	None	Central/pipelle
282-0571	RLX060	None	Central/pipelle
282-0959	RLX120	Promestriene	Central/pipelle
866-8732	RLX120	Premarin vaginal & Provera	Local/polypectomy=senile cystic atrophy
742-0334	RLX120	Estriol	Local/polypectomy = nos & atrophic endometrial cells

Hyperplastic polyps

Pt. #	Rx group	HRT/TAM use	Pathology site/procedure
003-3651	RLX060	Premarin/provera 1997	Central,1996/pipelle polyp = nos Central 1997 polypectomy=hyperplastic
032-2821	RLX060	None	Local/d&c = nos Central called it hyperplastic
063-4593	Placebo	Multiple estrogens used	Central/d&c
080-5058	RLX060	Prempro	Central/d&c

Functional polyps

Pt.#	Rx group	HRT/ TAM use	Pathology site/procedure
047-6668	RLX120	Premarin	Central/hysterectomy
068-6995	RLX060	None	Central/pipelle
071-0811	Placebo	None	Central/pipelle
077-4181	RLX060	None	Central/polypectomy
071-0631	RLX120	None	Central/pipelle

Polyps, not otherwise specified or simple

Pt. #	Rx group	HRT/ TAM use	Pathology site/procedure
052-8451	RLX060	None	Local/endom biopsy =nos
068-6939	RLX120	Cycrin	Central/pipelle =nos
071-0283	RLX120	Provera	Local/d&c= nos
805-6647	RLX060	None	Local/d&c= simple

No histologic confirmation, just sonogram diagnosis

Pt. #	Rx group	HRT/TAM use	Pathology
071-0291	Placebo	None	None
282-0907	RLX060	None	None

DRUDP Medical Officer comments:

If polyp formation is related to Evista, I would not expect the polyp to be atrophic in nature. Since I have no record of a baseline endometrial thickness by transvaginal ultrasound on this group of patients, I cannot say that the polyp formation occurred while on study drug. I would favor that most were pre-existing, especially the atrophic polyps.

Anecdotally, I have seen a few tamoxifen induced polyps that had a somewhat different histologic appearance than normally found.. Some of these polyps were sessile and very fibrous in nature. I have not heard of anything similar being reported by my colleagues for patients taking raloxifene.

Similar tables discussing the concomitant estrogen use and pathology details are needed to evaluate the patients who demonstrated an endometrial thickness greater than 5.0 mm. I would also like to know who was interpreting the sonogram (radiologist, gynecologist) and whether it might be a different interpreter on subsequent exams.

Does the sponsor have data showing a significant endometrial thickness change in patients solely on raloxifene (ie. > 5 mm increase above baseline)?

The use of small endometrial suction instruments like the Pipelle are excellent for many forms of endometrial diagnosis but are not very good for endometrial polyps. 10 of the above 25 evaluations depend on the pipelle for

diagnosis. If a small polyp is pulled into the Pipelle a pathologist can use architectural clues to establish that a polyp is present. If the polyp is large and only a small amount of the polyp is pulled in, you have to depend on seeing enough fibrosis and thick walled blood vessels to come up with the diagnosis and often then you should say suggestive of a polyp rather than being conclusive.

Studies that incorporate local pathologists suffer in that the local individual pathologist may not always look for the subtleties that a study evaluation requires. Diagnosis of simple polyp or "not otherwise specified" mainly occurred with local pathology diagnoses. If those polyps were really an atrophic type, they might also be pre-existing.

In the above table a definite histologic diagnosis of polyp was not recorded for pt. 866-8732. A patient scheduled for a polypectomy may or may not have histologic confirmation.

A question arises in the diagnoses that called the polyp functional. How was the term functional defined by the central pathologists? What glandular and mitotic features were required to make that determination?

The diagnosis of endometrial polyp by saline-infusion sonohysterography may not always be confirmed by biopsy. Some pedunculated leiomyomata could masquerade as a polyp. If a baseline normal sonogram was not found at study initiation, these polyps could also be pre-existing.

The study table GGGK.7.32 lists cervical polyps as cervical neoplasms. Many authors would disagree and consider cervical polyps as hamartomatous overgrowths, which in many cases may be secondary to inflammation. Microglandular hyperplasia can present as a polypoid growth and it is felt that this process is hormonally related. A data submission of the exact pathology diagnoses in addition to concomitant hormonal information should be requested from the sponsor to fully assess whether Evista is related to any cervical changes.

Assessment and recommendations:

I do not have enough data to provide a complete consultation on Evista and polyp formation. I will need additional information from HFD-510 or the sponsor to complete my review. I would like to request the following:

- Additional information on the transvaginal sonography protocols including information on personnel, baseline evaluations, exclusion of patients based on initial findings, and a pathology correlation of the patients showing significant endometrial thickness change over baseline levels.

- Detailed pathology, sonography and concomitant hormone use data in patients who had an endometrial thickness greater than 5mm who were subsequently diagnosed with endometrial polyps. These patients are found in Table GGGK. 7.23 and comprise 48 individuals.

- Detailed pathology data on those patients in Table GGGK 7.32 who are listed as having a cervix neoplasm (52 total patients)

- The histologic criteria for determining a polyp to be functional.

From the pathology data that I did review on the patients who reported bleeding, I am not convinced that Evista represents a risk for polyp development.

/S/ 8/4/99
Gerald Willett MD
Medical Officer
DRUDP- HFD 580

APPEARS THIS WAY
ON ORIGINAL

I Concur.
/S/ 8/4/99
Susan Allen, MD
Team Leader
DRUDP-HFD 580

APPEARS THIS WAY
ON ORIGINAL

LOT-LICATE

S-003

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

CENTER FOR DRUG
REC'D
SEP 29 1999
HFD-510
EVALUATION AND RESEARCH

September 28, 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 (sNDA) for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

Reference is made to the submission (September 21, 1999) of an NDA amendment which contained revisions to the draft Evista physician package insert. Reference is also made to an encrypted E-mail communication (September 24, 1999) from Mr. Randy Hedin to Dr. Paul Gesellchen which contained FDA recommendations for changes to the package insert. Please also refer to a videoconference (September 27, 1999) in which representatives of Eli Lilly and company and the FDA met to discuss the referenced September 24, 1999 recommendations.

We are herewith providing the final version of the Evista draft package insert as agreed to in the September 27, 1999 videoconference.

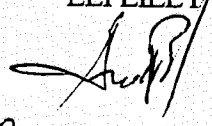
To assist the Agency in its review of these final modifications to the draft Evista package insert, we are providing two versions of the final draft label. In the first (marked-up) version (Attachment A) all additions to the draft version provided in the September 21, 1999 amendment have been highlighted by large, 18 point font while all deletions have been denoted by large, ~~18 point strikethroughs~~.

We are also providing a clean version of the draft package insert (Attachment B) in which all changes have been incorporated. This version of the draft Evista package insert supersedes all previous versions.

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 (HFD-510); cover letter only and one encrypted E-mail copy

DUPLICATE

NDA SUPP AMEND

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 27 1999
HFD-510

September 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

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 (June 11, 1999) of a revised patient package insert to the referenced NDA file and to a submission (September 15, 1999) of responses to FDA medical reviewer comments regarding the physician package insert.

Based on our acceptance of one specific FDA recommended changed to the physician package insert concerning monitoring of prothrombin time, we are proposing that the corresponding change be made to the patient package insert. We are also proposing two clarifying modifications to the text.

We are herewith providing the FDA with a revised "marked-up" version of the draft patient package insert (Attachment A) which contains the referenced modifications. We have utilized the patient package insert version that was submitted to the NDA file on June 11, 1999. We have modified the document by adding our proposed changes to the text (highlighted with a pink color in the electronic version; prints as dark gray on a black and white printer). We also have placed brief explanations of the proposed changes in boxes to the right of the affected label text.

We are also providing a "clean" version of the draft patient package insert (Attachment B) in which all changes have been incorporated. This version of the draft patient package insert supersedes all previous versions.

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, one encrypted E-mail copy, and 2 desk copies

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

September 21, 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 (sNDA) for the referenced drug product for the new indication of the treatment of osteoporosis in postmenopausal women.

Reference is also made to encrypted E-mail communications (September 15 and 20, 1999) from Mr. Randy Hedin (FDA) to Dr. Paul Gesellchen (Lilly). These communications contained recommended changes from the FDA Biopharmaceutics reviewer and the FDA Pharmacology reviewer, respectively, for the Evista package insert.

Finally, reference is made to amendments to the referenced sNDA (September 15 and 17, 1999) in which responses were made to FDA Medical Reviewer recommendations (September 10, 1999) for changes to the Evista package insert and to the FDA Division of Oncology Drug Product questions (September 15, 1999) regarding breast cancer data provided on August 24, 1999.

We are herewith providing the FDA with responses to the Biopharmaceutics reviewer recommended changes to the package insert that were described in the referenced E-mail communication of September 15, 1999. We also are providing our response to the changes recommended for the Animal Pharmacology section of the package insert, which were described in the referenced E-mail communication of September 20, 1999.

Based on a request from Mr. Hedin (September 17, 1999) to assist the Agency in its review of these modifications to the Evista package insert, all responses submitted to date (September 15 and 17, 1999) have been collated with the current responses, into one "marked-up" version of the draft physician package insert (Attachment A).

Note that changes to the package insert have been highlighted in various colors on the electronic copy (shades of gray on a black and white printer). For ease of reference, the color code is provided below and also is presented in the header of each page in the package insert.

FDA Medical Revisions 9/10/99	(yellow)
FDA Biopharm Revisions 9/15/99	(blue)
FDA Pharm Revisions 9/20/99	(green)
[redacted]	(pink)

Note that in the amendment submission of September 15, 1999, two minor changes to the package insert were inadvertently left out of that document. Those omissions have been incorporated in the current version of the package insert. Specifically, on page 15 of the enclosed draft package insert the word "statistically" has been deleted from the first footnote in Table 3 since the p-value is listed in the same footnote and is therefore redundant. On page 34 of the enclosed draft package insert the parenthetical phrase "(median of xx months)" should have been deleted as per the Lilly comments noted in the right hand margin of the September 15 submission.

We are also providing a "clean" version of the draft package insert (Attachment B) in which all changes have been incorporated. This version of the draft package insert supersedes all previous versions.

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 (HFD-510); cover letter only, one encrypted E-mail copy, and 12 desk copies