

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-520

CORRESPONDENCE

December 15, 2003

**General Correspondence
Electronic Edition of Responses to FDA Requests**

Central Document Room
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

**Re: NDA 21-520, SYMBYAX™ (olanzapine/fluoxetine combination) – Response to
FDA Questions**

Please find enclosed an electronic copy of responses to FDA questions received via e-mail on December 10 and 12, 2003 from Dr. Doris Bates. Responses to these questions were previously transmitted, via e-mail, to Dr. Doris Bates (FDA) on December 12, 2003.

The complete submission is provided in electronic format on one CD-ROM. The submission size less than 500 KB. All electronic media has been checked and verified to be free of known viruses. The virus checking software was Norton AntiVirus, corporate edition version 7.51.847, virus definition version 51210h, dated December 10, 2003.

Please call me at (317) 277-3554 if you have any questions or comments. Alternatively, you may call Dr. Gregory T. Brophy, Director of Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Patrick Burns, Pharm.D.
Regulatory Research Scientist
U.S. Regulatory Affairs

cc: Doris Bates, Ph.D. (cover letter)

**APPEARS THIS WAY
ON ORIGINAL**



Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2800

December 2, 2003

**General Correspondence
Electronic Edition of Responses to FDA Requests**

Central Document Room
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

**Re: NDA 21-520, SYMBYAX™ (olanzapine/fluoxetine combination) –
Response to FDA Questions**

Please find enclosed an electronic copy of responses to FDA questions received via e-mail on November 13, 2003 from Dr. Doris Bates. Responses to these questions were previously transmitted, via e-mail, to Dr. Doris Bates (FDA) on November 25, 2003.

The complete submission is provided in electronic format on one CD-ROM. The submission size less than 400 KB. All electronic media has been checked and verified to be free of known viruses. The virus checking software was Norton AntiVirus, corporate edition version 7.51.847, virus definition version 51119s, dated November 19, 2003.

Please call me at (317) 277-3554 if you have any questions or comments. Alternatively, you may call Dr. Gregory T. Brophy, Director of Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY


Patrick Burns, Pharm.D.
Regulatory Research Scientist
U.S. Regulatory Affairs

APPEARS THIS WAY
ORIGINAL

cc: Doris Bates, Ph.D. (cover letter)

www.lilly.com



Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

July 31, 2003

Responses to FDA Requests

Central Document Room
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

**Re: NDA 21-520, SYMBYAX™ (olanzapine/fluoxetine combination) – Response to
FDA Request**

Please find enclosed Lilly's responses to the e-mail request from Dr. Judith Racoosin received on July 16, 2003.

The complete submission is provided in electronic format on one CD-ROM. The submission size is approximately 1.5 MB. All electronic media has been checked and verified to be free of known viruses. The virus checking software was Norton AntiVirus, corporate edition version 7.51.847, virus definition version 50723p, dated July 23, 2003.

Please call me at (317) 277-3554 if you have any questions or comments. Alternatively, you may call Dr. Gregory T. Brophy, Director of Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Patrick Burns, Pharm.D.
Regulatory Research Scientist
U.S. Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

cc: Doris Bates, Ph.D. (cover letter)



7/8/03

NDA 21-520

Eli Lilly & Co., Inc.
Attention: Greg Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

We acknowledge receipt on June 25, 2003 of your June 24, 2003 resubmission to your new drug application for SYMBYAX (olanzapine and fluoxetine HCl) capsules.

We consider this a complete, class 2 response to our May 5, 2003 approvable action letter. Therefore, the user fee goal date for this submission is December 25, 2003.

If you have any questions, please call the undersigned, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug
Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Electronic CC to: Dr. Patrick Burns

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

7/8/03 01:45:37 PM

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June 24, 2003

**Complete Response to FDA
Approvable Letter: NDA 21-520**

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 21-520, Symbyax™ (Olanzapine and Fluoxetine Combination)

Enclosed, please find an electronic copy of the Complete Response to the Priority Review Approvable letter for Symbyax™ for the treatment of Depressive episodes associated with bipolar disorder, dated May 5, 2003.

We request that you review our complete response as a PDUFA Class 1 resubmission. Additionally, we request a meeting or teleconference to finalize labeling and any other steps to approval.

The complete submission is provided in electronic format on a single CD-ROM. The submission size approximately 34 MB. All electronic media has been checked and verified to be free of known viruses. The virus checking software was Norton AntiVirus, corporate edition version 7.51.847, virus definition version 50681f, dated June 18, 2003.

Please call me at (317) 277-3554 if you have any questions or comments. Alternatively, you may call Dr. Gregory T. Brophy, Director of Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Patrick Burns, Pharm.D.
Regulatory Research Scientist
U.S. Regulatory Affairs

cc: Doris Bates, Ph.D. (cover letter)

APPEARS THIS WAY
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Olanzapine and Fluoxetine HCl
Symbyax™
NDA 21-520

Regulatory Response: Note to Reviewer

Complete Response to Approvable Letter

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ON ORIGINAL

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1. Complete Response to the Approvable Letter Olanzapine/ Fluoxetine for the Treatment of Depressive Episodes Associated with Bipolar Disorder

1.1. Background

On November 4, 2002, Lilly submitted a new drug application (NDA 21-520) for the use of the olanzapine/fluoxetine combination for the treatment of depressive episodes associated with Bipolar disorder. Receipt of the application was confirmed on November 5, 2002, and Priority review status was confirmed by the FDA on December 2, 2002. The Division of Neuropharmacological Drug Products subsequently deemed the application approvable in a letter dated May 5, 2003. Subsequent to the receipt of the approvable letter, Lilly notified the FDA of our intent to amend the application on May 14, 2003.

Lilly considers this submission to constitute a Complete Response to the approvable letter. Additionally, Lilly requests the FDA review this response under PDUFA as a Class 1 resubmission based on the following:

- Due to the lack of approved medications for the treatment of depressive episodes associated with Bipolar disorder, a 2-month review would be consistent with the spirit of the priority review of the initial application.
- The primary focus of the Complete Response is on proposed labeling.
- The additional safety analyses and patient follow-up information requested in the approvable letter does not alter our conclusions and serves to clarify questions and supports the proposed labeling. While this response may initially appear voluminous, please note that a significant portion this response consists of hand-generated vital sign tables related to orthostatic hypotension. These tables have been included specifically to provide additional evidence for the conclusions stated in the fairly brief sections of text. Every effort has been made to present the responses to the requested analyses in a very user-friendly manner to facilitate the ease of the clinical review.
- Discussions with the Department of Scientific Investigations (Dr. Viswanathan) indicated that inspectional activities our clinical pharmacology site in Singapore may be completed within the 2-month review timeframe.

• 7

• 7

1.2. Structure of the Complete Response

The complete response is presented in the format of an amendment to NDA 21-520. This Note to Reviewer refers to sections as listed in the amendment table of contents. In general, the note to reviewer addresses issues in the order of their appearance in the approvable letter, followed by the issues embedded within the FDA proposed package insert.

Where Lilly's responses to the FDA proposed package insert wording are brief, they are included within the comment boxes in the attached revised version of the package insert. Lengthier responses to comments or questions from within the FDA proposed package insert are linked to a specific document within this response.

1.3. Response to Comments and Requests in the Approvable Letter

A. Proposed Trademark

Lilly understands that the proposed proprietary name Symbyax™ will be re-evaluated prior to the approval of the application. As requested in the approvable letter, a complete set of mock-up container labels and labeling, featuring the trademark, are included in Item 2 of this response.

B. Chemistry Manufacturing and Controls (CMC)

1. Lilly agrees to the changes proposed to revise the list of excipients in the package insert. Please refer to the package insert contained in Item 2.
2. Lilly agrees to revise the storage statement and to incorporate that statement into the package insert and container labeling. Please refer to the package insert and container labeling contained in Item 2.

C. CMC: Other Issues

D. Nonclinical Pharmacology and Toxicology (complete responses included in Item 5)

Proposed Phase 4 commitments:

1. Prenatal/postnatal development study in Rats: Lilly believes the incidence of testicular degeneration observed from the low-dose OFC combination arm in the Symbyax perinatal/postnatal study is consistent with background incidence observed in control groups. Therefore, we contend that a repeat perinatal/postnatal study to determine a NOAEL is not warranted.

2.

E. Clinical Pharmacology and Biopharmaceutics (complete responses included in Items 4 and 6)

1. Dissolution testing: Lilly believes that tightening the dissolution specification is unnecessary; a dissolution specification of Q = — at 30 minutes provides ample quality assurance control for the release and monitoring of all Symbyax capsules and requests to retain the originally submitted dissolution method and specification for all strengths of olanzapine/fluoxetine hydrochloride capsules.
2. Proposed Phase 4 Commitment; CYP1A2: Lilly has previously conducted a study with fluvoxamine, a potent CYP1A2 inhibitor and therefore contends that an additional CYP1A2 inhibitor drug interaction study will not substantially change the information or dose recommendation in the product labeling. Therefore, Lilly requests that the Division not require a additional CYP1A2 drug interaction study as a Phase 4 commitment.

F. Clinical / Statistical / Clinical Safety (complete responses included in Item 8)

As requested in the May 5, 2003 Approvable letter, included is a comprehensive review and discussion supporting the lack of a fluoxetine-only treatment arm in the bipolar depression study.

Also included are Lilly's responses to comments and requests for clinical safety information as outlined in Items 1-10 within the Clinical / Statistical / Clinical Safety section of the May 5th Approvable letter.

G. Request for Safety Update

As agreed upon in the 22 May 2003 and 03 June 2003 e-mail correspondences with the Division, the following safety update information is provided:

1. Study F1D-MC-HGIE, serious adverse event, discontinuation due to adverse event, and treatment-emergent adverse event validated data since the 2-month safety update. Narratives for all deaths, serious adverse events, and discontinued due to adverse events for HGIE that have been previously submitted. The final data lock for this study was 09 December 2002.

2. Narratives from validated data for all deaths, serious adverse events, and discontinued due to adverse events for Study H6P-MC-HDAO. The data cut-off date was 22 May 2003.
3. Narratives from validated data for all deaths, serious adverse events, and discontinued due to adverse events for Study H6U-MC-HGLL. The data cut-off date was 04 June 2003.
4. A World literature update is provided within Item 9.
5. Worldwide regulatory update: Since Lilly's original NDA submission to the FDA, no other regulatory action or filings have been taken.

Labeling (Package Insert and Container Labeling)

1. Draft labeling with responses to FDA proposed revisions and label mock-ups are presented in Item 2 of this response.
2. As requested in the approvable letter, Lilly has provided a Patient Package Insert (PPI) with the revised labeling. The PPI is also presented in Item 2.
3. Lilly has made the following changes to the labels and container labeling as requested in the approvable letter. Specifically, Lilly has:
 - Heightened the contrast of the 12/25 dosage form container labeling to improve legibility.
 - Included the revised storage statement to correspond the wording in the package insert.
 - Modified the yellow portion of the "X" has so that it does not interfere the readability of the tradename.
 - Included the dose form in the established name.
 - Included the "mg" designation for each dosage strength. For example the revised 6/25 mg Symbyax label now reads "6mg / 25mg".
 - Modified the color scheme of the  dosage and 6 mg / 50 mg dosage.
 - Modified the background contrast for the 12 mg/ 25 mg and 6 mg / 25 mg labels to enhance the readability of the text.

H. Promotional Materials

Lilly has not yet completed development of introductory promotional materials. Lilly will submit these materials at the time of first use, consistent with CFR 314.81.

1.4. Responses to Comments from the Annotated FDA Proposed Package Insert

Within the FDA proposed package insert, the following subjects are addressed:

- A. Pharmacokinetics
- B. Clinical Studies
- C. Cerebrovascular Adverse Events
- D. Orthostatic hypotension
- E. Tremor
- F. Hyponatremia
- G. Platelet Dysfunction/Abnormal Bleeding
- H. Transaminase elevations
- I. Weight gain
- J. QTc
- K. Impairment of Fertility and Pregnancy
- L. Adverse events

1.5. Lilly requests a meeting or teleconference to discuss proposed changes

Lilly request a meeting or teleconference with the FDA to discuss proposed changes in labeling content or format and final steps to approval of this application at the earliest practical time.

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2.0 Attachments

APPEARS THIS WAY
ON ORIGINAL

Note to Reviewer: Attachment A

As with the original submission of NDA 21-520, this attachment clarifies the location of the COSTART classification terms for this submission. The table also includes those terms that have been excluded from Table 3, Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies and/or footnotes to Tables 3, or from Additional Findings observed in Clinical Studies.

The following table lists all COSTART classification terms reflecting a treatment-emergent adverse event in the primary database for OFC. The terms are ordered Alphabetically by Body System and Event. The reasons any event term excluded is summarized below, and will be referred to in the following table by the shorthand term described below:

1. Redundant (REDNT)

The Adverse Event is listed elsewhere in labeling

2. Uninformative (UNINF)

The Adverse Event term so general as to be uninformative

3. Remote (REMTE)

The Adverse Event for which a drug cause was judged remote

4. One and not life threatening (1RULE)

The Adverse Event was reported in only one patient, and there was not a substantial probability of that event being acutely life threatening

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OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
1) TABLE	BODY AS A WHOLE	ACCIDENTAL INJURY			3%	
		ASTHENIA			15%	
		FEVER			3%	
	CARDIOVASCULAR SYSTEM	HYPERTENSION			2%	
		TACHYCARDIA			2%	
	DIGESTIVE SYSTEM	DIARRHEA			8%	
		DRY MOUTH			11%	
		INCREASED APPETITE			16%	
	METABOLIC AND NUTRITIONAL DISORDERS	EDEMA			5%	
		PERIPHERAL EDEMA			8%	

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
1) TABLE	METABOLIC AND NUTRITIONAL DISORDERS	WEIGHT GAIN			21%	
		MUSCULOSKELETAL SYSTEM	ARTHRALGIA			3%
		TWITCHING			2%	
	NERVOUS SYSTEM	AMNESIA			3%	
		HYPERKINESIA			1%	
		LIBIDO DECREASED			2%	
		PERSONALITY DISORDER			1%	
		SLEEP DISORDER			1%	
		SOMNOLENCE			22%	

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
1) TABLE	NERVOUS SYSTEM	THINKING ABNORMAL			6%	
		TREMOR			8%	
	RESPIRATORY SYSTEM	DYSPNEA			2%	
		PHARYNGITIS			6%	
	SPECIAL SENSES	AMBLYOPIA			4%	
		EAR PAIN			1%	
		OTITIS MEDIA			0%	
	UROGENITAL SYSTEM	ABNORMAL EJACULATION			2%	
		ANORGASMIA			1%	
		IMPOTENCE			2%	

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
2) FOOT	BODY AS A WHOLE	ABDOMINAL PAIN			2%	
		BACK PAIN			4%	
		CHEST PAIN			2%	
		FLU SYNDROME			3%	
		HEADACHE			12%	
		PAIN			6%	
	CARDIOVASCULAR SYSTEM	PALPITATION			2%	
	DIGESTIVE SYSTEM	ANOREXIA			1%	
		CONSTIPATION			4%	
		DYSPEPSIA			6%	
		FLATULENCE			3%	

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Po1 DB/OFC	P/I	
			Sum	P/I	P/I	Sum	
2) FOOT	DIGESTIVE SYSTEM	NAUSEA			7%		
		VOMITING			3%		
	MUSCULOSKELETAL SYSTEM	MYALGIA			5%		
		NERVOUS SYSTEM	ABNORMAL DREAMS			3%	
			AGITATION			4%	
			AKATHISIA			3%	
			ANXIETY			8%	
			APATHY			2%	
			DEPRESSION			4%	
			DIZZINESS			9%	
			HYPERTONIA			2%	

(CONTINUED)
RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Po1 DB/OFC	P/I
			Sum	P/I	P/I	Sum
2) FOOT	NERVOUS SYSTEM	INSOMNIA			6%	
		MANIC REACTION			1%	
		NERVOUSNESS			9%	
		PARESTHESIA			3%	
	RESPIRATORY SYSTEM	COUGH INCREASED			2%	
		RHINITIS			5%	
		SINUSITIS			3%	
	UROGENITAL SYSTEM	DYSMENORRHEA			1%	
	SKIN AND APPENDAGES	SWEATING			3%	
	3) LIST	BODY AS A WHOLE	DEATH	2	0%	

(CONTINUED)
RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	BODY AS A WHOLE	TOLERANCE DECREASED	2	0%		2
		MONILIASIS	3	0%		3
		MALAISE	5	0%		5
		PELVIC PAIN	5	0%		5
		HERNIA	6	0%		6
		INTENTIONAL INJURY	6	0%		6
		CELLULITIS	8	0%		8
		INTENTIONAL OVERDOSE	8	0%		8
		OVERDOSE	8	0%		8
		CYST	9	0%		9

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I	
			Sum	P/I	P/I	Sum	
3) LIST	BODY AS A WHOLE	SUICIDE ATTEMPT	16	1%		16	
		PHOTOSENSITIVITY REACTION	22	1%		22	
		NECK RIGIDITY	24	1%		24	
		CHILLS	26	1%		26	
		NECK PAIN	30	1%		30	
		INFECTION	67	3%		67	
		CARDIOVASCULAR SYSTEM	ANGINA PECTORIS	1	0%		1
			ATRIAL ARRHYTHMIA	1	0%		1
			MYOCARDIAL INFARCT	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	CARDIOVASCULAR SYSTEM	ATRIAL FIBRILLATION	2	0%		2
		BUNDLE BRANCH BLOCK	2	0%		2
		CONGESTIVE HEART FAILURE	2	0%		2
		PERIPHERAL VASCULAR DISORDER	2	0%		2
		T INVERTED	2	0%		2
		BRADYCARDIA	4	0%		4
		CEREBRAL ISCHEMIA	4	0%		4
		HYPOTENSION	6	0%		6

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RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	CARDIOVASCULAR SYSTEM	QT INTERVAL PROLONGED	6	0%		6
		ARRHYTHMIA	8	0%		8
		ELECTROCARDIOGR- AM ABNORMAL	13	1%		13
		VASODILATATION	24	1%		24
		MIGRAINE	25	1%		25
	DIGESTIVE SYSTEM	GASTROINTESTINAL HEMORRHAGE	1	0%		1
		INTESTINAL OBSTRUCTION	1	0%		1
		PANCREATITIS	1	0%		1
		APHTHOUS STOMATITIS	2	0%		2

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evs	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	DIGESTIVE SYSTEM	FECAL INCONTINENCE	2	0%		2
		GUM HEMORRHAGE	2	0%		2
		LIVER FATTY DEPOSIT	2	0%		2
		COLITIS	3	0%		3
		ERUCTION	3	0%		3
		HEPATOMEGALY	3	0%		3
		PEPTIC ULCER	3	0%		3
		CHOLELITHIASIS	5	0%		5
		ESOPHAGITIS	6	0%		6
		GASTRITIS	7	0%		7

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evs	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	DIGESTIVE SYSTEM	NAUSEA AND VOMITING	7	0%		7
		STOMATITIS	7	0%		7
		TOOTH CARIES	7	0%		7
		GINGIVITIS	8	0%		8
		PERIODONTAL ABSCESS	11	1%		11
		GASTROENTERITIS	12	1%		12
		INCREASED SALIVATION	28	1%		28
		THIRST	28	1%		28
		TOOTH DISORDER	35	2%		35

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	METABOLIC AND NUTRITIONAL DISORDERS	BILIRUBINEMIA	1	0%		1
		HYPOGLYCEMIC REACTION	1	0%		1
		ACIDOSIS	2	0%		2
		CREATININE INCREASED	2	0%		2
		GOUT	2	0%		2
		HYPERKALEMIA	2	0%		2
		HYPOGLYCEMIA	3	0%		3
		HYPOKALEMIA	3	0%		3
		ALCOHOL INTOLERANCE	4	0%		4
		HYPERLIPEMIA	7	0%		7

(CONTINUED)
RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	METABOLIC AND NUTRITIONAL DISORDERS	DEHYDRATION	9	0%		9
		OBESITY	9	0%		9
		GENERALIZED EDEMA	22	1%		22
		WEIGHT LOSS	23	1%		23
		HYPERGLYCEMIA	30	1%		30
	MUSCULOSKELETAL SYSTEM	ARTHROSIS	2	0%		2
		BURSITIS	2	0%		2
		MYASTHENIA	2	0%		2
		MYOPATHY	2	0%		2
		OSTEOPOROSIS	2	0%		2

(CONTINUED)
RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	MUSCULOSKELETAL SYSTEM	RHEUMATOID ARTHRITIS	2	0%		2
		BONE DISORDER	3	0%		3
		GENERALIZED SPASM	3	0%		3
		TENDINOUS CONTRACTURE	3	0%		3
		TENOSYNOVITIS	5	0%		5
		ARTHRITIS	15	1%		15
		LEG CRAMPS	18	1%		18
		JOINT DISORDER	62	3%		62
		NERVOUS SYSTEM	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	NERVOUS SYSTEM	SUBARACHNOID HEMORRHAGE	1	0%		1
		WITHDRAWAL SYNDROME	1	0%		1
		ACUTE BRAIN SYNDROME	2	0%		2
		APHASIA	2	0%		2
		LIBIDO INCREASED	2	0%		2
		COMA	3	0%		3
		MYOCLONUS	3	0%		3
		COGWHEEL RIGIDITY	5	0%		5
		EXTRAPYRAMIDAL SYNDROME	5	0%		5

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	NERVOUS SYSTEM	DYSARTHRIA	6	0%		6
		NEUROSIS	6	0%		6
		NEURALGIA	7	0%		7
		VERTIGO	7	0%		7
		BUCCOGLOSSAL SYNDROME	9	0%		9
		EUPHORIA	10	0%		10
		HYPOKINESIA	10	0%		10
		ABNORMAL GAIT	11	1%		11
		ATAXIA	11	1%		11
		HYPESTHESIA	13	1%		13

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	NERVOUS SYSTEM	MOVEMENT DISORDER	14	1%		14
		EMOTIONAL LABILITY	16	1%		16
		DEPERSONALIZATI- ON	17	1%		17
		HOSTILITY	17	1%		17
		INCOORDINATION	18	1%		18
		CONFUSION	20	1%		20
	RESPIRATORY SYSTEM	LARYNGISMUS	1	0%		1
		EMPHYSEMA	2	0%		2
		HEMOPTYSIS	2	0%		2
		HICCUP	5	0%		5

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	RESPIRATORY SYSTEM	HYPERVENTILATION	5	0%		5
		LARYNGITIS	6	0%		6
		VOICE ALTERATION	6	0%		6
		YAWN	7	0%		7
		PNEUMONIA	13	1%		13
		ASTHMA	15	1%		15
		APNEA	16	1%		16
		EPISTAXIS	19	1%		19
		LUNG DISORDER	29	1%		29
		BRONCHITIS	38	2%		38
	SPECIAL SENSES	EYE HEMORRHAGE	2	0%		2

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	SPECIAL SENSES	MIOSIS	2	0%		2
		DEAFNESS	3	0%		3
		DIPLOPIA	3	0%		3
		EYE PAIN	5	0%		5
		ABNORMALITY OF ACCOMMODATION	8	0%		8
		CONJUNCTIVITIS	9	0%		9
		DRY EYES	10	0%		10
		TINNITUS	21	1%		21
		TASTE PERVERSION	23	1%		23
		ABNORMAL VISION	54	3%		54

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	UROGENITAL SYSTEM	GYNECOMASTIA	0	0%		0
		BREAST ENGORGEMENT	1	0%		1
		ENDOMETRIAL DISORDER	1	0%		1
		BREAST CARCINOMA	2	0%		2
		HYPOMENORRHEA	2	0%		2
		KIDNEY CALCULUS	2	0%		2
		MENOPAUSE	2	0%		2
		UTERINE FIBROIDS ENLARGED	2	0%		2
		GLYCOSURIA	3	0%		3
		OLIGURIA	3	0%		3

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	UROGENITAL SYSTEM	OVARIAN DISORDER	3	0%		3
		BREAST NEOPLASM	4	0%		4
		FIBROCYSTIC BREAST	4	0%		4
		HEMATURIA	4	0%		4
		LEUKORRHEA	4	0%		4
		URINATION IMPAIRED	4	0%		4
		VAGINAL MONILIASIS	4	0%		4
		CYSTITIS	6	0%		6
		FEMALE LACTATION	6	0%		6

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	UROGENITAL SYSTEM	URINARY RETENTION	6	0%		6
		VAGINAL HEMORRHAGE	6	0%		6
		BREAST ENLARGEMENT	7	0%		7
		DYSURIA	8	0%		8
		AMENORRHEA	9	1%		9
		POLYURIA	10	0%		10
		VAGINITIS	13	1%		13
		METRRORRHAGIA	14	1%		14
		URINARY URGENCY	15	1%		15
		MENORRHAGIA	18	1%		18

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I	
			Sum	P/I	P/I	Sum	
3) LIST	UROGENITAL SYSTEM	URINARY INCONTINENCE	22	1%		22	
		BREAST PAIN	23	1%		23	
		URINARY FREQUENCY	35	2%		35	
		URINARY TRACT INFECTION	42	2%		42	
		SKIN AND APPENDAGES	EXFOLIATIVE DERMATITIS	2	0%		2
			MACULOPAPULAR RASH	2	0%		2
	SEBORRHEA		2	0%		2	
	SKIN ULCER		2	0%		2	

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	SKIN AND APPENDAGES	VESICULOBULLOUS RASH	3	0%		3
		PSORIASIS	4	0%		4
		SKIN DISCOLORATION	4	0%		4
		CONTACT DERMATITIS	6	0%		6
		ECZEMA	7	0%		7
		DRY SKIN	10	0%		10
		ACNE	15	1%		15
		ALOPECIA	16	1%		16
		PRURITUS	20	1%		20

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3)LIST	ENDOCRINE SYSTEM	DIABETIC ACIDOSIS	1	0%		1
		HYPOTHYROIDISM	4	0%		4
		DIABETES MELLITUS	20	1%		20
	HEMIC AND LYMPHATIC SYSTEM	COAGULATION DISORDER	1	0%		1
		LEUKOPENIA	1	0%		1
		PURPURA	1	0%		1
		THROMBOCYTHEMIA	2	0%		2
		LEUKOCYTOSIS	4	0%		4
		LYMPHADENOPATHY	6	0%		6
		ANEMIA	12	1%		12

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
3) LIST	HEMIC AND LYMPHATIC SYSTEM	ECCHYMOSIS	24	1%		24
4) 1 RULE	BODY AS A WHOLE	ABDOMEN ENLARGED	1	0%		1
		ACCIDENTAL OVERDOSE	1	0%		1
		ADENOMA	1	0%		1
		BODY ODOR	1	0%		1
		CARCINOMA	1	0%		1
		HANGOVER EFFECT	1	0%		1
		HORMONE LEVEL ALTERED	1	0%		1
		HYDROCEPHALUS	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4) 1 RULE	BODY AS A WHOLE	INJECTION SITE HEMORRHAGE	1	0%		1
		LACK OF DRUG EFFECT	1	0%		1
		NEOPLASM	1	0%		1
		REACTION UNEVALUABLE	1	0%		1
		SCLERODERMA	1	0%		1
	CARDIOVASCULAR SYSTEM	AV BLOCK FIRST DEGREE	1	0%		1
		CARDIOMEGALY	1	0%		1
		DEEP THROMBOPHEBITIS	1	0%		1
		HEMORRHAGE	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4) 1 RULE	CARDIOVASCULAR SYSTEM	LEFT HEART FAILURE	1	0%		1
		MYOCARDIAL ISCHEMIA	1	0%		1
		THROMBOPHLEBITIS	1	0%		1
		VARICOSE VEIN	1	0%		1
		VASCULAR ANOMALY	1	0%		1
		VASCULAR DISORDER	1	0%		1
	DIGESTIVE SYSTEM	ABNORMAL STOOLS	1	0%		1
		BILIARY PAIN	1	0%		1
		CARDIOSPASM	1	0%		1
		CHOLECYSTITIS	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4) 1 RULE	DIGESTIVE SYSTEM	ESOPHAGEAL STENOSIS	1	0%		1
		GLOSSITIS	1	0%		1
		HEMORRHAGIC GASTRITIS	1	0%		1
		MELENA	1	0%		1
		MOUTH ULCERATION	1	0%		1
		RECTAL HEMORRHAGE	1	0%		1
		SALIVARY GLAND ENLARGEMENT	1	0%		1
		TENESMUS	1	0%		1
		TOOTH MALFORMATION	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4)1 RULE	DIGESTIVE SYSTEM	ULCERATIVE STOMATITIS	1	0%		1
	METABOLIC AND NUTRITIONAL DISORDERS	ACID PHOSPHATASE INCREASED	1	0%		1
		BUN INCREASED	1	0%		1
		HEALING ABNORMAL	1	0%		1
		HYPERCALCEMIA	1	0%		1
	MUSCULOSKELETAL SYSTEM	BONE PAIN	1	0%		1
		MYOSITIS	1	0%		1
		OSTEOMYELITIS	1	0%		1
	NERVOUS SYSTEM	ABNORMAL ELECTROENCEPHAL- OGRAM	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4)1 RULE	NERVOUS SYSTEM	AKINESIA	1	0%		1
		DELUSIONS	1	0%		1
		FACIAL PARALYSIS	1	0%		1
		HYPERESTHESIA	1	0%		1
		HYPOTONIA	1	0%		1
		NEUROPATHY	1	0%		1
		REFLEXES INCREASED	1	0%		1
		RESPIRATORY SYSTEM	CARCINOMA OF LUNG	1	0%	
	PLEURAL DISORDER		1	0%		1
	SPECIAL SENSES	BLEPHARITIS	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4)1 RULE	SPECIAL SENSES	CATARACT NOS	1	0%		1
		CATARACT SPECIFIED	1	0%		1
		CORNEAL LESION	1	0%		1
		KERATITIS	1	0%		1
		PHOTOPHOBIA	1	0%		1
		RETINAL HEMORRHAGE	1	0%		1
		TASTE LOSS	1	0%		1
		VESTIBULAR DISORDER	1	0%		1
		VISUAL FIELD DEFECT	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4)1 RULE	UROGENITAL SYSTEM	ALBUMINURIA	1	0%		1
		BLADDER NEOPLASM	1	0%		1
		CERVICITIS	1	0%		1
		CERVIX CARCINOMA	1	0%		1
		ENDOMETRIAL HYPERPLASIA	1	0%		1
		KIDNEY PAIN	1	0%		1
		NEPHRITIS	1	0%		1
		NOCTURIA	1	0%		1
		POLYCYSTIC KIDNEY	1	0%		1
		PROSTATIC DISORDER	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4) 1 RULE	UROGENITAL SYSTEM	TESTIS DISORDER	1	0%		1
		URETHRAL PAIN	1	0%		1
		UROGENITAL DISORDER	1	0%		1
		UTERINE HEMORRHAGE	1	0%		1
	SKIN AND APPENDAGES	EPIDERMAL NECROLYSIS	1	0%		1
		ERYTHEMA NODOSUM	1	0%		1
		FURUNCULOSIS	1	0%		1
		HIRSUTISM	1	0%		1
		PUSTULAR RASH	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
4) 1 RULE	SKIN AND APPENDAGES	SKIN BENIGN NEOPLASM	1	0%		1
		SKIN HYPERTROPHY	1	0%		1
	ENDOCRINE SYSTEM	ADRENAL DISORDER	1	0%		1
		THYROID DISORDER	1	0%		1
	HEMIC AND LYMPHATIC SYSTEM	HYPOCHROMIC ANEMIA	1	0%		1
		LYMPHOCYTOSIS	1	0%		1
		MACROCYTIC ANEMIA	1	0%		1
		MICROCYTIC ANEMIA	1	0%		1
		PETECHIA	1	0%		1

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
5) REDUND	BODY AS A WHOLE	FACE EDEMA	24	1%		24
		ALLERGIC REACTION	43	2%		43
	CARDIOVASCULAR SYSTEM	SINUS BRADYCARDIA	3	0%		3
		SYNCOPE	18	1%		18
		POSTURAL HYPOTENSION	37	2%		37
	DIGESTIVE SYSTEM	HYPERCHLORHYDRIA	2	0%		2
		STOMACH ULCER	2	0%		2
		DYSPHAGIA	5	0%		5
		GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	9	0%		9

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
5) REDUND	DIGESTIVE SYSTEM	TONGUE EDEMA	10	0%		10
		LIVER FUNCTION TESTS ABNORMAL	22	1%		22
	METABOLIC AND NUTRITIONAL DISORDERS	HYPONATREMIA	1	0%		1
		ALKALINE PHOSPHATASE INCREASED	2	0%		2
		HYPERURICEMIA	2	0%		2
		SGPT INCREASED	6	0%		6
		SGOT INCREASED	7	0%		7
		CREATINE PHOSPHOKINASE INCREASED	13	1%		13

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
5) REDUND	METABOLIC AND NUTRITIONAL DISORDERS	HYPERCHOLESTERE- MIA	22	1%		22
	NERVOUS SYSTEM	CONVULSION	2	0%		2
		GRAND MAL CONVULSION	2	0%		2
		SPEECH DISORDER	29	1%		29
	RESPIRATORY SYSTEM	RESPIRATORY DISORDER	14	1%		14
	SPECIAL SENSES	REFRACTION DISORDER	2	0%		2
	UROGENITAL SYSTEM	URINARY TRACT DISORDER	3	0%		3
		MENSTRUAL DISORDER	17	1%		17

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
5) REDUND	SKIN AND APPENDAGES	RASH			3%	
		HAIR DISORDER	2	0%		2
		URTICARIA	6	0%		6
	ENDOCRINE SYSTEM	PROLACTIN INCREASED	9	0%		9
6) REMOTE	CARDIOVASCULAR SYSTEM	SHOCK	1	0%		1
	DIGESTIVE SYSTEM	HEPATITIS B POSITIVE SA	2	0%		2
	NERVOUS SYSTEM	ADDICTION	2	0%		2
		MULTIPLE SCLEROSIS	2	0%		2
		PSYCHOTIC DEPRESSION	2	0%		2

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
6) REMOTE	NERVOUS SYSTEM	PSYCHOSIS	5	0%		5
		PARANOID REACTION	7	0%		7
		DRUG DEPENDENCE	12	1%		12
		HALLUCINATIONS	15	1%		15
	SPECIAL SENSES	OTITIS EXTERNA	3	0%		3
	UROGENITAL SYSTEM	UNINTENDED PREGNANCY	6	0%		6
	SKIN AND APPENDAGES	HERPES ZOSTER	3	0%		3
		HERPES SIMPLEX	4	0%		4
		FUNGAL DERMATITIS	8	0%		8
		NAIL DISORDER	8	0%		8

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
7) UNINFR	BODY AS A WHOLE	SURGICAL PROCEDURE			2%	
		MUCOUS MEMBRANE DISORDER	2	0%		2
		ABSCESS	3	0%		3
		LAB TEST ABNORMAL	8	0%		8
		UNEXPECTED BENEFIT	25	1%		25
	CARDIOVASCULAR SYSTEM	CARDIOVASCULAR DISORDER	5	0%		5
	DIGESTIVE SYSTEM	RECTAL DISORDER	3	0%		3
		TONGUE DISORDER	3	0%		3

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
7) UNINFR	DIGESTIVE SYSTEM	GASTROINTESTINAL DISORDER	18	1%		18
	MUSCULOSKELETAL SYSTEM	TENDON DISORDER	5	0%		5
	SPECIAL SENSES	LACRIMATION DISORDER	2	0%		2
		EAR DISORDER	6	0%		6
		EYE DISORDER	19	1%		19
	UROGENITAL SYSTEM	KIDNEY FUNCTION ABNORMAL	1	0%		1
		URINE ABNORMALITY	3	0%		3
	SKIN AND APPENDAGES	SKIN DISORDER	2	0%		2

(CONTINUED)

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

OFC Package Insert
OFC Controlled Trials

TESS			OFC Evts	OFC	Pol DB/OFC	P/I
			Sum	P/I	P/I	Sum
7) UNINFR	SKIN AND APPENDAGES	SUBCUTANEOUS NODULE	2	0%		2

RMP.H6PSREG1.SASPGM(LBLW01PL) 85266

APPEARS THIS WAY
ON ORIGINAL

www.lilly.com

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

May 14, 2003

Notification of Intent to Amend NDA

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Woodmont Building, No. II
Attn.: Document Division Room
1451 Rockville Pike
Rockville, MD 20852-1448

Re: SymbyaxTM – (olanzapine/fluoxetine HCL – LY900000) – Notification of Intent to Amend NDA 21-520

Pursuant to the provisions of 21 CFR 314.110 and the instructions in your 05 May 2003 approvable letter for the referenced NDA, please be advised of our intent to file an amendment in response to that approvable letter.

Thank you for your ongoing cooperation and assistance. If you have any questions, please feel free to call me at (317) 277-3554 or call Dr. Gregory T. Brophy, Director of US Regulatory Affairs at (317) 277-3799.

Sincerely,

ELI LILLY AND COMPANY

Patrick Burns

Patrick Burns, Pharm.D.
Regulatory Research Scientist,
U.S. Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Bates, Doris J

From: BURNS_PATRICK_R@LILLY.COM
Sent: Tuesday, December 09, 2003 4:50 PM
To: Bates, Doris J
Cc: Racoosin, Judith A; BURNS_PATRICK_R@LILLY.COM; Bates, Doris J; Hammad, Tarek
Subject: RE: NDA 21,520 Symbyax: A Labeling Question (URGENT)

Dr Bates,

In responding to the Agency's request that any "face edema" cases consistent with angioedema be described in the Warnings statement of allergic events and rash (refer to Lines 1165 to 1167 of the package insert in the May 5, 2003 approvable letter) we reviewed all potential cases of face and/or tongue edema in the OFC database. Patient HGGA-1206 discontinued due to the adverse event of face edema and is the second case of discontinuation due to a possible allergic adverse event . No other cases were identified.

For completeness the one page patient summary for HGGA-1206 is included in with this message and can be found in Appendix 5.2.2 One page patient Summaries, pages 1203 and 1204 of the HGGA abbreviated study report included in the original submission of NDA 21520 (submitted on Nov 4, 2002)

I have copied Drs. Racoosin and Hammad as you suggested. Please let me know if you have any problems opening the attachment or are not able to locate the patient summary in the HGGA abbreviated report

Patrick Burns, Pharm.D.
 Eli Lilly and Company
 U.S. Regulatory Affairs
 Phone 317-277-3554
 Pager 866-476-5207

"Bates, Doris J"

<BATESD@cder.fda.gov>

12/08/2003 04:14 PM

To: "Bates, Doris J" <BATESD@cder.fda.gov>, "BURNS_PATRICK_R@LILLY.COM" <BURNS_PATRICK_R@LILLY.COM>
 cc: "Hammad, Tarek" <HammadT@cder.fda.gov>, "Racoosin, Judith A" <RACOOSINJ@cder.fda.gov>
 Subject: Clean Copy RE: NDA 21,520 Symbyax: A Labeling Question (URGENT)

My original transmission included an earlier email thread. This is a clean copy of the current FDA question only.

-----Original Message-----

From: Bates, Doris J
Sent: Monday, December 08, 2003 4:11 PM
To: 'BURNS_PATRICK_R@LILLY.COM'; Bates, Doris J
Cc: Hammad, Tarek; Racoosin, Judith A
Subject: RE: NDA 21,520 Symbyax: A Labeling Question (URGENT)
Importance: High

Good afternoon Pat:

Our clinical safety reviewer has noted in the Symbyax label that under the "Warnings" section (sub-section

12/10/2003

"allergic events and rash"), your labeling discusses three patients that discontinued, one with rash and two with allergic reactions. We found the rash patient (HGIP-001-1014) and one of the allergic reaction patients (HGIP-007-1334) in the submission. Can you please point us to the location of the information about the second case of allergic reaction that discontinued? Adding the second case of allergic reactions was one of the modifications you had proposed on the label.

Thanks in advance – we do need this information rather urgently – and the text is excerpted below for your reference. An e-mail response will suffice for this question as long as no new information is provided (i.e., directions to existing information in submission only). Please feel free to CC Drs. Racoosin and Hammad on any response.

Allergic events and rash — In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic events in SYMBYAX–treated patients, 4.6% (26/571), was similar to that of placebo, 5.2% (25/477). The majority of the events were mild; 3 patients discontinued (one due to rash, which was moderate in severity, and 2 due to allergic events which included face and/or tongue edema).

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Protocol: F1D-MC-HGGA

Reason for Summary:
Discontinuations due to Adverse
Event

Patient: (12) 1206

Study Medication: Olanzapine and Fluoxetine

Randomization: 26OCT1998

Age: 48.0

Sex: Male

Origin: Caucasian

Weight: 88.90 kg

Event: Actual Term – Facial Edema
Class Term – Face Edema
Severity – Moderate
Serious? - No

Onset from initial therapy: 176

Abnormal Labs (Last available abnormal lab)

Analyte	Result	Unit	Lo Limit	Hi Limit
AST	103	U/L	11.000	79.000
ALT	140	U/L	7.000	125.000
CHOL	8.84	mmol/L	2.840	8.560
T.BILI	<3	umol/L	3.000	31.000

Adverse Events:

Classification Term (Actual)	Onset	Relative Onset	Duration
Apnea (sleep apnea)	⌈	⌈ -3220	-
Rectal Disorder (hemmoroids)	⌈	⌈ 0	1
Pruritus (itching feet)	⌈	⌈ 0	127
Insomnia (insomnia)	⌈	⌈ 2	-

Concomitant Medications

Drug	Start Date	Stop Date
Preparation H	⌈	⌈
Tinactin	⌈	⌈
Ativan	⌈	⌈

Hydrochlorothiazide

20APR1999

04MAY1999

Summary:

Patient's first visit was 20OCT1998. Patient was randomized to olanzapine and fluoxetine treatment on 26OCT1998. Patient reported facial edema on [redacted] and was discontinued at Visit 308 on [redacted] by the investigator and followed for resolution of the adverse event until Follow-up Visit 501 on [redacted]. Patient had 204 days of olanzapine and fluoxetine at the time of discontinuation. At the time of onset, the patient had been in open-label phase 118 days. At the time of follow-up, the adverse event of facial edema had resolved. In the investigator's opinion, the event of facial edema was possibly related to study drug.

APPEARS THIS WAY
ON ORIGINAL

Bates, Doris J

From: Patrick R Burns [BURNS_PATRICK_R@LILLY.COM]
Sent: Thursday, December 18, 2003 11:57 AM
To: Racoosin, Judith A
Cc: Bates, Doris J; Hammad, Tarek
Subject: Re: Point of clarification

Dr. Racoosin

We are responding to your request for clarifications;

1. FDA question: In reference to Table 1 on p. 5 of the 12/12/03 submission, the table includes data for olz, flx, and pbo arms in addition to the OFC dose arms. The "N"s for the olz and flx arms don't match the ones in the study report for HGIE.

Lilly Response: Table 1 from the 12/12/03 submission is a combination of HGIE patients for the 4 OFC arms and the entire pooled database for the comparator arms. If information is needed regarding only HGIE patients, that is available in Table HGIE.12.23 of the HGIE Clinical Study Report. However, the correction factor used in generating that table was 0.47.

2. FDA question: Additionally, HGIE did not have a placebo arm (unless the low dose 1/5 is being considered a placebo). Please explain where the data for these three arms is coming from.

Lilly response: You are correct, Study HGIE did not include a placebo arm. In developing our response we used the pooled controlled database (6 studies) and excluded all patients not on the fixed doses used in HGIE.

3. FDA question: Additionally, we found an analysis in your original NDA submission (section 10.4.2.4) that included a dose-response analysis of the QTc data in HGIE. The mean changes from baseline included in that analysis ("the mean QTc interval increase from baseline to endpoint using Regression correction for OFC 6/25, 6/50, 12/25, and 12/50 was 6.4 ± 19.5 , 6.9 ± 15.5 , 1.6 ± 18.0 , and 3.2 ± 23.3 ms, respectively") don't match the ones included in Table 1. Please explain the source of the discrepancy.

Lilly Response. The numbers reported in the HGIE study report were calculated using a the 0.47 regression factor. The numbers reported in the December 12th response for HGIE were calculated using the 0/41 regression factor to be consistent with other submission.

Patrick Burns, Pharm.D.
Eli Lilly and Company
U.S. Regulatory Affairs
Phone 317-277-3554
Pager 866-476-5207

"Racoosin, Judith A"
<RACOOSINJ@cder.fda.gov>

12/17/2003 05:26 PM

To: "BURNS_PATRICK_R@LILLY.COM" <BURNS_PATRICK_R@LILLY.CO
cc: "Bates, Doris J" <BATESD@cder.fda.gov>, "Hammad, Tarek"

<HammadT@cder.fda.gov>
Subject: Point of clarification

Good afternoon Dr. Burns,
In reference to Table 1 on p. 5 of the 12/12/03 submission, the table includes data for olz, flx, and pbo arms in addition to the OFC dose arms. The "N"s for the olz and flx arms don't match the ones in the study

12/18/2003

report for HGIE.

Additionally, HGIE did not have a placebo arm (unless the low dose 1/5 is being considered a placebo). Please explain where the data for these three arms is coming from.

Additionally, we found an analysis in your original NDA submission (section 10.4.2.4) that included a dose-response analysis of the QTc data in HGIE. The mean changes from baseline included in that analysis ("the mean QTc interval increase from baseline to endpoint using Regression correction for OFC 6/25, 6/50, 12/25, and 12/50 was 6.4 ± 19.5 , 6.9 ± 15.5 , 1.6 ± 18.0 , and 3.2 ± 23.3 ms, respectively") don't match the ones included in Table 1. Please explain the source of the discrepancy.

Thanks!

Judy Racoosin

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/s/

Doris Bates
12/18/03 01:23:51 PM
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Bates, Doris J

From: BURNS_PATRICK_R@LILLY.COM
Sent: Friday, December 12, 2003 5:58 PM
To: BatesD@cder.fda.gov
Cc: Racoosin, Judith A; Hammad, Tarek
Subject: RE: NDA 21,520 Symbyax: Response to the additional requests.

Dr. Bates,

Attached is our response to questions received via e-mail on December 10th and 12th. As you suggested I have copied Drs. Racoosin and Hammad on this message. I will formally submit the information on Monday December 15th.

Please let me know if you have any problems opening the file.

Thank you.

Patrick Burns, Pharm.D.
Eli Lilly and Company
U.S. Regulatory Affairs
Phone 317-277-3554
Pager 866-476-5207

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12/15/2003

Bates, Doris J

From: Bates, Doris J
Sent: Friday, December 12, 2003 5:48 PM
To: Bates, Doris J
Subject: FW: NDA 21,520 Symbyax: one additional request

-----Original Message-----

From: Racoosin, Judith A
Sent: Friday, December 12, 2003 9:13 AM
To: 'BURNS_PATRICK_R@LILLY.COM'; Bates, Doris J
Cc: Racoosin, Judith A; Bates, Doris J; Hammad, Tarek
Subject: RE: NDA 21,520 Symbyax: one additional request

Good Morning Dr. Burns,
Doris has not yet arrived this morning, and I did not want to delay getting this question to you.

Using the case definition for "injury/fall" that you used for the 12/2/03 submission, please provide the incidence of "injury/fall" for each of the treatment groups in the OFC pooled database.

Thanks!

Judy Racoosin

Judy Racoosin, MD, MPH
Safety Team Leader
Division of Neuropharmacological Drug Products
Tel: 301-594-2850
Fax: 301-594-2858
E-mail: racoosinj@cder.fda.gov

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/s/

Doris Bates

12/12/03 05:48:01 PM

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sent to firm by Dr. Racoosin on 12.12.03 at
9:13 a.m; checked into DFS by RPM.

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Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, December 10, 2003 3:33 PM
To: 'BURNS_PATRICK_R@LILLY.COM'; Bates, Doris J
Cc: Racoosin, Judith A; Hammad, Tarek
Subject: RE: NDA 21,520 Symbyax: A Labeling Question (URGENT)

Good afternoon Pat:

I am forwarding a question from Dr. Racoosin. Please feel free to CC both her and Dr. Hammad on the response, to minimize any possible delay in their receipt of the information.

The Safety Review team is having difficulty finding the tables or analyses that presented the mean change from baseline for the QTcR41(regression 41) for the OFC group in the OFC pooled database broken out by dose group (6/25, 6/50, 12/50). Table 21 from the 12/16/02 submission shows the summary mean change from baseline for the OFC group. Please point us to the location of this dose-stratified data in the NDA, or provide it if it was not included.

Additionally, please point us to the location of or provide the categorical change in QTcR41 for the OFC group in the OFC pooled database broken out by dose group (6/25, 6/50, 12/50), based on the categories shown in Table 22 from the 12/16/02 submission.

Additionally, please point us to the location of or provide the PCS changes in QTcR41 for the OFC group in the OFC pooled database broken out by dose group (6/25, 6/50, 12/50), based on the categories shown in Table 26 from the 12/16/02 submission.

As always, feel free to respond via secure e-mail; we will need a copy submitted to the EDR if new information is included in that response, but not if you only need to point us to information already contained in the submission.

Regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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12/10/2003

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/s/

Doris Bates
12/10/03 03:33:12 PM
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Bates, Doris J

From: Bates, Doris J
Sent: Monday, December 08, 2003 4:14 PM
To: Bates, Doris J; 'BURNS_PATRICK_R@LILLY.COM'
Cc: Hammad, Tarek; Racoosin, Judith A
Subject: Clean Copy RE: NDA 21,520 Symbyax: A Labeling Question (URGENT)

My original transmission included an earlier email thread. This is a clean copy of the current FDA question only.

-----Original Message-----

From: Bates, Doris J
Sent: Monday, December 08, 2003 4:11 PM
To: 'BURNS_PATRICK_R@LILLY.COM'; Bates, Doris J
Cc: Hammad, Tarek; Racoosin, Judith A
Subject: RE: NDA 21,520 Symbyax: A Labeling Question (URGENT)
Importance: High

Good afternoon Pat:

Our clinical safety reviewer has noted in the Symbyax label that under the "Warnings" section (sub-section "allergic events and rash"), your labeling discusses three patients that discontinued, one with rash and two with allergic reactions. We found the rash patient (HGIP-001-1014) and one of the allergic reaction patients (HGIP-007-1334) in the submission. Can you please point us to the location of the information about the second case of allergic reaction that discontinued? Adding the second case of allergic reactions was one of the modifications you had proposed on the label.

Thanks in advance – we do need this information rather urgently – and the text is excerpted below for your reference. An e-mail response will suffice for this question as long as no new information is provided (i.e., directions to existing information in submission only). Please feel free to CC Drs. Racoosin and Hammad on any response.

Allergic events and rash — In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic events in SYMBYAX-treated patients, 4.6% (26/571), was similar to that of placebo, 5.2% (25/477). The majority of the events were mild; 3 patients discontinued (one due to rash, which was moderate in severity, and 2 due to allergic events which included face and/or tongue edema).

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
12/8/03 04:16:28 PM
CSO

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Bates, Doris J

From: Bates, Doris J
Sent: Thursday, November 13, 2003 3:53 PM
To: 'BURNS_PATRICK_R@LILLY.COM'
Cc: Racoosin, Judith A; Hammad, Tarek; Bates, Doris J
Subject: Nov 13, 2003: Requests regarding Symbyax response to the approvable letter

Good afternoon Pat,

Our clinical safety team has some questions on the resubmission at this point. They have formatted them as point-by-point items, citing the relevant Lilly submission and then presenting the questions. I've attached a .pdf file of the questions – please let me know if you have difficulty opening or printing.

I will be out of the office on December 4 and 5, and may be out one day Thanksgiving week (besides thanksgiving) – so you may wish to respond to Drs. Racoosin and Hammad directly, with a CC to me, to avoid delays. (An e-mail response with a follow-up submission to the EDR will be fine.)

Thanks as always,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Additional requests for OFC 11/13/03

Safety update (June 20, 2003 submission)

- There are 204 new spontaneous AEs reported with the combined use of olanzapine and fluoxetine since the cut-off date for the original NDA submission (Jan 31, 2002). Please provide an update on the deaths and serious adverse events reported in this newer group of reports.

Lilly's response to FDA request 7A

3.2.2.1.1 Patients with a Concomitant Decrease in Orthostatic Pulse and Orthostatic Blood Pressure (Response 7a Bullet 1)

- Please provide the incidence of a ≥ 1 bpm decrease in orthostatic pulse and a concomitant >20 mmHg or >30 mmHg decrease in orthostatic systolic blood pressure for each of the study arms in the OFC pooled database (i.e., OFC, olanzapine, fluoxetine, placebo)
- Provide the incidence of AEs consisting of injuries (e.g., lacerations, bruises, fractures) and/or falls for each of the study arms in the OFC pooled database (i.e., OFC, olanzapine, fluoxetine, placebo) among patients with a ≥ 1 bpm decrease in orthostatic pulse and a concomitant >20 mmHg or >30 mmHg decrease in orthostatic systolic blood pressure. Please search verbatim terms to identify such AEs because they may be coded to a variety of preferred terms beyond "accidental injury". The incidence of SAEs should also be reported.
 - For the patients in each study arm that had an injury and/or fall, please provide a line listing of the preferred term and verbatim term (along with patient ID and study) of the AE.
- In this section you state that "Of the 37 patients (with a ≥ 1 bpm decrease in orthostatic pulse and a concomitant >20 mmHg or >30 mmHg decrease in orthostatic systolic blood pressure), at the visit where criteria were met, the pulse decrease was <5 bpm for 16 of the patients and between 5 and 10 bpm for an additional 9 of the patients (p. 23, RESPONSE_6-7.pdf, 20 June 2003 submission).
 - What was the SBP decrease and associated pulse decrease for the remaining 12 patients (please include patient ID number)?

In the summary for the response to 7a Bullet 1, it states that 20 patients had a decrease in pulse >10 bpm (p. 136, RESPONSE_6-7.pdf, 20 June 2003 submission). The statement above suggests that 12 patients had a decrease of pulse >10 bpm.

- Why is there a discrepancy between the numbers of patients in these two statements? If there are 20 patients meeting that criterion (decrease of pulse >10 bpm), please include the additional eight in the response to the bullet above.
- Among these patients (either 12 or 20 depending on which statement above is correct) that had the most marked decrease in pulse (≥ 10

bpm) associated with the fall in systolic blood pressure, did any have associated AEs consisting of injuries (e.g., lacerations, bruises, fractures) and/or falls? Please search verbatim terms to identify such AEs because they may be coded to a variety of preferred terms beyond “accidental injury”.

- Provide a line listing of the preferred term and verbatim term (along with patient ID and study) of the AE (should be a subset of the line listing above)
- At the time Patient HGFR-01-1005 had a syncopal episode between visits 6 and 7 and orthostatic VS changes of decreased pulse of 30 bpm and a decreased systolic BP of 23 mmHg at visit 7, what OFC dose was she taking? Was there a dose adjustment after the orthostatic VS changes were noted?

3.2.2.1.2 Patients with Adverse Events Possibly Related to Orthostatic Hypotension (Response 7a Bullet 2)

- For each of the six subgroups (e.g., possible syncope, decreased BP + decreased pulse, etc.) described in this section, please provide the incidence among each of the study arms in the OFC pooled database (i.e., OFC, olanzapine, fluoxetine, placebo). The incidence of SAEs should also be reported.
 - For the patients in each study arm that had “possible syncope”, please provide a line listing of the preferred term and verbatim term of the AE that qualified them as having had “possible syncope”
- Among the patients in the three categories of possible syncope, decreased BP + decreased pulse, and decreased BP + no change in pulse, provide the incidence of AEs consisting of injuries (e.g., lacerations, bruises, fractures) and/or falls for each of the study arms in the OFC pooled database (i.e., OFC, olanzapine, fluoxetine, placebo). Please search verbatim terms to identify such AEs because they may be coded to a variety of preferred terms beyond “accidental injury”. The incidence of SAEs should also be reported.
 - Provide a line listing of the preferred term and verbatim term (along with patient ID and study) of the AE

3.2.2.1.3 Patients with Adverse Events Possibly Related to Bradycardia (Response 7a Bullet 3)

- Among the patients who met one or more of the criteria for bradycardia, provide the incidence of AEs consisting of injuries (e.g., lacerations, bruises, fractures) and/or falls for each of the study arms in the OFC pooled database (i.e., OFC, olanzapine, fluoxetine, placebo). Please search verbatim terms to identify such AEs because they may be coded to a variety of preferred terms beyond “accidental injury”. The incidence of SAEs should also be reported.
 - Provide a line listing of the preferred term and verbatim term (along with patient ID and study) of the AE

Bates, Doris J

From: Racoosin, Judith A
Sent: Wednesday, July 16, 2003 4:12 PM
To: BURNS_PATRICK_R (E-mail)
Cc: Hammad, Tarek; Racoosin, Judith A; Bates, Doris J
Subject: Requests regarding Symbyax response to the approvable letter

Good afternoon, Dr. Burns,

Please submit the following items to assist our review of the response to the approvable letter.

Thanks

Judy Racoosin

Judy Racoosin, MD, MPH
Safety Team Leader
Division of Neuropharmacological Drug Products
Tel: 301-594-2850
Fax: 301-594-2858
E-mail: racoosinj@cdcr.fda.gov

1. Safety update (reference section 3.1.1.2)

- Provide a brief description of the study design of HDAO
- Provide line listings for the SAEs and discontinuations due to AEs in HDAO
- Provide frequencies for the SAEs and discontinuations due to AEs in HDAO (we know it is still blinded)

2. Response 6_7.pdf

- Bookmark all patient narratives in the response to 7-A.
- Provide line listings for the patients in the response to 7-A, organized by their corresponding databases (e.g., "acute bipolar depressed", "overall bipolar depressed", "OFC pooled database", or "2 month safety update"). Note: we recognize that a patient in the "acute bipolar depressed" database would also be in the other three databases, but the line listings should be organized such that a patient is listed in the most narrowly defined applicable database.
- Provide rates by treatment group based on person-years for concomitant orthostatic hypotension and bradycardia in the acute bipolar-depression database.
- Please provide rates for the following tables under section 7-B: 8, 9, 12-17, 20-27

3. Note to Reviewer

- Please elaborate on the intent of the table in Attachment "A". Also, please explain the abbreviations used. The first page of the attachment references a "Table 3: Treatment Emergent AEs: Incidence in Controlled Clinical Studies". Where is the location of this Table 3- are you referring to labeling? Is the expectation that the "redundant" terms will not be presented? We do not agree that all the terms you've labeled that way are "redundant" (e.g. "face edema" and "allergic reaction")

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Doris Bates

7/16/03 04:16:11 PM

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Placed in DFS by RPM; transmitted to firm by
Dr. Racoosin at time shown on e-mail.

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Bates, Doris J

From: Bates, Doris J
Sent: Tuesday, July 08, 2003 11:09 AM
To: Katz, Russell G; Andreason, Paul J; Oliver, Thomas F; Racoosin, Judith A; Hammad, Tarek; Uppoor, Ramana S; Yasuda, Sally; Tabacova, Sonia; Hsieh, Li Shan; Freed, Lois M
Cc: Bates, Doris J
Subject: Summary of Meeting: SYMBYAX NDA 21-520 Resubmission Evaluation for Completeness of Response

Drs. Katz, Andreason, Racoosin, Hammad, Yasuda and Bates were present. Information was provided in advance from Drs. Oliver, Hsieh, Freed, and Tabacova.

Overall the submission is considered a complete response. CMC, Pharm/Tox, and Biopharm expect to be able to complete reviews within two months. The clinical portion of the labeling review can also be completed within two months.

However, due to the large volume of information, much of it new, which has been provided in response to the clinical safety questions (10 questions with ca. 25 subcomponents; over 400 pp. of responses including ca. 40 patient narratives), the package does not qualify as a Class 1 resubmission. It is therefore a Class 2 resubmission, with a six month action due date of December 25, 2003.

- The DSI inspection of the Singapore pivotal bioequivalence study will be initiated at the end of July.
- DMETS has noted the similarity of the SYMBYAX and CYMBALTA trademarks; the alternative trademark ' _____ (for duloxetine in SUI) has been discussed with them.
- []

Meeting participants agreed that those reviews which could be completed to a two month clock should still be done in that time frame, to enable the Division to take action as soon as realistically possible within the overall six month time frame. The Clinical Safety Review Team is preparing a set of questions for the firm, to be forwarded shortly.

This summary will be placed in DFS as the minutes of this meeting.

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/s/

Doris Bates
7/8/03 11:14:47 AM

JH 01/10/03

Bates, Doris J

From: Oliver, Thomas F
Sent: Monday, July 07, 2003 1:44 PM
To: Bates, Doris J
Cc: Hsieh, Li Shan
Subject: Symbiax

Doris,

The sponsor has responded to each of the CMC issues. Li-Shan will evaluate their responses in review #2. As discussed, Li-Shan and I will not be attending tomorrow's meeting.

Thanks again,
Tom

APPEARS THIS WAY
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Bates, Doris J

From: Oliver, Thomas F
Sent: Monday, July 07, 2003 1:52 PM
To: Bates, Doris J
Cc: Hsieh, Li Shan
Subject: RE: Symbiax

As it is probably obvious--a 2 month clock for CMC.

Thanks,
Tom

-----Original Message-----

From: Bates, Doris J
Sent: Monday, July 07, 2003 1:47 PM
To: Oliver, Thomas F
Cc: Hsieh, Li Shan
Subject: RE: Symbiax

Thanks for the input, Tom, and I wish you as good a week as possible in the circumstances.

Li-Shan, you know we appreciate your help. I'm glad I can show some of that appreciation by giving you a little bit of your time back; you definitely don't need to come to the meeting.

I will email everybody with the final decision as to whether we have a two or six month clock on this.

take care,

Doris

-----Original Message-----

From: Oliver, Thomas F
Sent: Monday, July 07, 2003 1:44 PM
To: Bates, Doris J
Cc: Hsieh, Li Shan
Subject: Symbiax

Doris,

The sponsor has responded to each of the CMC issues. Li-Shan will evaluate their responses in review #2. As discussed, Li-Shan and I will not be attending tomorrow's meeting.

Thanks again,
Tom

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Bates, Doris J

Subject: SYMBYAX NDA 21-520 Resubmission Evaluation for Completeness of Response
Location: CDER WOC2 3FL-C Conf Room

Start: Tue 7/8/2003 10:00 AM
End: Tue 7/8/2003 10:30 AM

Recurrence: (none)

Meeting Status: Meeting organizer

Required Attendees: Bates, Doris J; Katz, Russell G; Andreason, Paul J; Oliver, Thomas F; Racoosin, Judith A; Hammad, Tarek; Uppoor, Ramana S; Yasuda, Sally; Tabacova, Sonia; Hsieh, Li Shan; Freed, Lois M

Resources: CDER WOC2 3FL-C Conf Room

Please note that this meeting is scheduled in Conference Room C on the Third Floor. Our Conference Room was not available.

This meeting has been placed on the calendar on June 18, 2003. Lois, I know you are out that day and I am very sorry. The firm is expecting to send its complete response to our action letter on June 25, which is next Wednesday. July 8 is Day 14 if the submission is received on the 25th. I was unable to find any time when all participants were available that would fall within the 14 day deadline.

June 25, 2003: The submission was indeed received on this date.

We will need to inform the firm

whether this is a complete response

whether it is a class 1 or class 2 resubmission

after this meeting.

This is going to be an all electronic submission. I will receive courtesy copies by email of the cover letter, the proposed labeling, and a summary of the responses (Note to Reviewer), which I will attach to this meeting notice when received.

thanks all for your patience. this is the only way to meet these assessment deadlines. I will send consults out for stats and biopharm as soon as I have the courtesy copies in hand.

**APPEARS THIS WAY
ON ORIGINAL**

Bates, Doris J

om: Tabacova, Sonia
ent: Wednesday, July 02, 2003 11:33 AM
To: Bates, Doris J
Cc: Freed, Lois M; Rosloff, Barry N
Subject: RE: SYMBYAX NDA 21-520 Resubmission Evaluation for Completeness of Response

Doris. the pharmtox response looks complete.

The decision about the class of the resubmission will depend on the clinical reviewers because the pharmtox issues are fewer. We could do it as a Class I resubmission.

Sorry I won't be able to attend the meeting on July 8.

Sonia

-----Original Message-----

From: Bates, Doris J
Sent: Wednesday, June 18, 2003 4:16 PM
To: Tabacova, Sonia
Subject: RE: SYMBYAX NDA 21-520 Resubmission Evaluation for Completeness of Response

No problem, I'll just need to know from you or Lois that the pharmtox response looks complete. Lois is out the day of this meeting, so we won't have anyone there from pharmtox, so I will just need an opinion via email some time beforehand.

-----Original Appointment-----

From: Tabacova, Sonia
Sent: Wednesday, June 18, 2003 4:13 PM
To: Bates, Doris J
Subject: Declined: SYMBYAX NDA 21-520 Resubmission Evaluation for Completeness of Response
When: Tuesday, July 08, 2003 10:00 AM-10:30 AM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER WOC2 3FL-C Conf Room

Doris, I'll be out of office on July 7 through 9 - have a dental surgery, quite nasty. Sorry.
Sonia

APPEARS THIS WAY
ON ORIGINAL

Bates, Doris J

From: BURNS_PATRICK_R@LILLY.COM
Sent: Friday, March 21, 2003 3:46 PM
To: BatesD@cder.fda.gov
Cc: BURNS_PATRICK_R@LILLY.COM
Subject: NDA 21520 Change in the spelling of the proposed tradename

Doris,

Following the submission of the new Symbiax labeling artwork on February 27, 2003, we learned of an objection from Abbott Laboratories to the use of Symbiax as the trademark for the olanzapine/fluoxetine combination. Abbott's objection was that the "biax" portion of Symbiax was too similar to their antibiotic trademark Biaxin. Over the past two weeks we have been in negotiations with Abbott's trademark counsel and have agreed that changing the "i" to a "y" would be acceptable to both parties. Hence the spelling will change from SYMBIAX to SYMBYAX.

Because of the short timeframe to the May 5th action date, only about 7 weeks, I am attaching a PDF file (Symbyax.pdf) of the new spelling artwork for your consideration. The only change to the presentations submitted on February 27, 2003 will be the substitution of Symbyax for Symbiax, no other changes will be made.

Please let me know if you have any questions.

Patrick Burns, Pharm.D.
Eli Lilly and Company
U.S. Regulatory Affairs
Phone 317-277-3554
Pager 866-476-5207

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ON ORIGINAL

3/21/2003

1 page(s) of draft labeling has been removed from this portion of the review.

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this page is the manifestation of the electronic signature.**

/s/

Doris Bates
3/21/03 06:26:22 PM
CSO

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ON ORIGINAL

Bates, Doris J

From: Bates, Doris J
Sent: Friday, March 21, 2003 4:59 PM
To: 'BURNS_PATRICK_R@LILLY.COM'
Subject: Clinical Safety Review Questions, NDA 21-520, March 21, 2003

Dear Dr. Burns:

Attached is a .pdf file summarizing review questions from our Clinical Safety team for NDA 21-520. The attachment, in combination with this e-mail cover message, may be treated as official agency correspondence.

I will be out of the office for part of the day on Monday, but should be available after 2:00 P.M. that day. Please feel free to contact me with any questions you may have on this correspondence.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

SYMBYAX (NDA 21-520)
Clinical Safety Questions
March 21, 2003

We are completing the clinical safety review of NDA 21520 (Symbyax) and have the following questions:

- 1- We are having trouble locating the overdose section in the ISS of OFC. Can you please point us to its location?
- 2- Upon reviewing the coding for edema, peripheral edema and face edema, we noticed that there is overlap in the mapping of verbatim terms to these three preferred terms. We request that you please re-code these verbatim terms in a consistent manner and report the corrected frequencies.
- 3- After re-coding edema-related events as mentioned earlier in "point 2", please check on the profile of patients that reported edema/peripheral edema as an adverse event to look for concomitant AEs suggestive of congestive heart failure. This should be done for all treatment groups.
- 4- Please provide follow-up information for the following patients:
 - Patient HGIE-017-1807: Did the patient have a VQ scan or other test looking for a pulmonary embolism? If so, what were the results?
 - Patient HGHZ-051-3503: Following discontinuation of OFC, did the patient have to stay on insulin or any other anti-diabetic therapy?
 - Patient HGIE-613-6358: Following discontinuation of OFC, did the patient have to stay on insulin or any other anti-diabetic therapy?
 - Patient HGIP-015-1716: While continuing on OFC (following discharge from the hospital, did the patient have to stay on insulin or any other anti-diabetic therapy?
 - Patient HGIP-015-1706: Which "cardiac arrhythmia" was the patient diagnosed with during the hospital admission? Did the patient continue on OFC therapy following discharge?
- 5- Please provide the overall rate of death, serious AE, and AE leading to dropout for each treatment group (this was in your original ISS submission, but was not recalculated for the 12/16/02 submission).
- 6- In table 32 (submission dated 12/16/2002) you are presenting the rates for treatment-emergent suicide attempt or ideation. Please provide separate rates for these two events.

Please indicate an approximate time for provision of a consolidated response to the above items. We are able to accept a Review Aid copy of this response via secure e-mail concomitantly with submission of an identical amendment to the NDA file.

If you have any questions, please feel free to contact Doris J. Bates, Ph.D., at 301-594-5536 or via secure email at batesd@cder.fda.gov.

APPROVED FOR RELEASE
ON 01/11/2011

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this page is the manifestation of the electronic signature.**

/s/

Doris Bates

3/21/03 05:07:37 PM

CSO

Sent to company on same date as DFS signature.
See first page for actual time of transmission
to firm.

APR 1 2003 11:11 AM
U.S. DISTRICT COURT

Bates, Doris J

From: Patrick R Burns [BURNS_PATRICK_R@LILLY.COM]
Sent: Tuesday, December 23, 2003 3:54 PM
To: Bates, Doris J
Subject: RE: NDA 21-520: Symbyax PI and PPI: FDA Proposed Versions of December 23, 2003 --- Impotence Information

Doris,

The attached file provides the support for excluding impotence from the **Commonly observed adverse events in controlled clinical**. We would appreciate the Division reviewing the table. However, should there not be anyone to review the table we would not want to hold an approval for this cycle.

We are working on the label and the Phase 4 now and I hope to be able to get back to you before 6PM.

Thanks Doris

Patrick Burns, Pharm.D.
Eli Lilly and Company
U.S. Regulatory Affairs
Phone 317-277-3554
Pager 866-476-5207

"Bates, Doris J"

<BATESD@cdcr.fda.gov>

12/23/2003 01:57 PM

To: "Patrick R Burns" <BURNS_PATRICK_R@LILLY.COM>

cc: "Bates, Doris J" <BATESD@cdcr.fda.gov>

Subject: RE: NDA 21-520: Symbyax PI and PPI: FDA Proposed Versions of December 23, 2003

Pat, here are the FDA versions from today - finally -- !

Doris J. Bates, Ph.D.

Regulatory Project Manager

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

12/24/2003

[attachment "Clean FDA 12_23_03 PI.doc" has been removed by Patrick R Burns/AM/LLY]

[attachment "PPI 122203 changes on 121003 DNDP version.doc" has been removed by Patrick R Burns/AM/LLY]

**Appears This Way
On Original**

Treatment Emergent Adverse Events
 Bipolar Depression ISS - Acute Phase
 All Databases and Therapies combined
 Gender-specific events only

Classification Term	OFC			Event Rate
	N	n	%	
DYSMENORRHEA **	406	6	1	0.0976
MENSTRUAL DISORDER **	406	6	1	0.0976
ABNORMAL EJACULATION *	165	4	2	0.1574
IMPOTENCE *	165	4	2	0.1574
MENORRHAGIA **	406	4	1	0.0651
AMENORRHEA **	406	2	0	0.0325
LEUKORRHEA **	406	2	0	0.0325

Event rate is per patient year.

OFC = Olanzapine + Fluoxetine, FLX = Fluoxetine, OLZ = Olanzapine, PLA = Placebo

* Denominator used was for males only, ** = ... females only

RMP.H6PSISSB.SASPGM(POLTESS) X7690

Output is RMP.H6PO.ISS2(POLTESSG)

NOT TO BE USED
 UNLESS NECESSARY

Treatment Emergent Adverse Events
 Bipolar Depression ISS - Acute Phase
 All Databases and Therapies combined
 Gender-specific events only

Classification Term	OFC			
	N	n	%	Event Rate
METrorrhagia **	406	2	0	0.0325
VAGINITIS **	406	2	0	0.0325
CERVICITIS **	406	1	0	0.0163
FEMALE LACTATION **	406	1	0	0.0163
FIBROCYSTIC BREAST **	406	1	0	0.0163
HYPOMENORRHEA **	406	1	0	0.0163

Event rate is per patient year.

OFC = Olanzapine + Fluoxetine, FLX = Fluoxetine, OLZ = Olanzapine, PLA = Placebo

* Denominator used was for males only, ** = ... females only

RMP.H6PSISSB.SASPGM(POLTESS) X7690

Output is RMP.H6PO.ISS2(POLTESSG)

01.01.2011

Treatment Emergent Adverse Events
 Bipolar Depression ISS - Acute Phase
 All Databases and Therapies combined
 Gender-specific events only

Classification Term	OFC			Event Rate
	N	n	%	
VAGINAL HEMORRHAGE **	406	1	0	0.0163
PROSTATIC DISORDER *	165	0	0	0.0000
TESTIS DISORDER *	165	0	0	0.0000
UNINTENDED PREGNANCY **	406	0	0	0.0000

Event rate is per patient year.

OFC = Olanzapine + Fluoxetine, FLX = Fluoxetine, OLZ = Olanzapine, PLA = Placebo

* Denominator used was for males only, ** = ... females only

RMP.H6PSISSB.SASPGM(POLTESS) X7690

Output is RMP.H6PO.ISS2(POLTESSG)

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Treatment Emergent Adverse Events
 Bipolar Depression ISS - Acute Phase
 All Databases and Therapies combined
 Gender-specific events only

Classification Term	FLX							OLZ							PLA						
	N	n	%	Event Rate	Ratio of Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI	N	n	%	Event Rate	Ratio of Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI	N	n	%	Event Rate	Ratio of Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI
DYSMENORRHEA **	192	4	2	0.1468	0.665	0.158	3.202	422	9	2	0.1791	0.545	0.160	1.714	284	10	4	0.3444	0.283	0.085	0.860
MENSTRUAL DISORDER **	192	1	1	0.0367	2.659	0.323	122.3	422	3	1	0.0597	1.634	0.349	10.10	284	5	2	0.1722	0.567	0.144	2.347
ABNORMAL EJACULATION *	59	2	3	0.2149	0.732	0.105	8.094	263	2	1	0.0635	2.477	0.355	27.39	193	1	1	0.0538	2.923	0.289	143.9
IMPOTENCE *	59	0	0	0.0000	UNDF	0.242	UNDF	263	4	2	0.1270	1.239	0.231	6.650	193	2	1	0.1077	1.461	0.209	16.15
MENORRHAGIA **	192	2	1	0.0734	0.886	0.127	9.797	422	2	0	0.0398	1.634	0.234	18.07	284	0	0	0.0000	UNDF	0.312	UNDF

Event rate is per patient year.

OFC = Olanzapine + Fluoxetine, FLX = Fluoxetine, OLZ = Olanzapine, PLA = Placebo

* Denominator used was for males only, ** = ... females only

RMP.H6PSISSB.SASPGM(POLTESS) X7690

Output is RMP.H6PO.ISS2(POLTESSG)

Treatment Emergent Adverse Events
 Bipolar Depression ISS - Acute Phase
 All Databases and Therapies combined
 Gender-specific events only

Classification Term	FLX							OLZ							PLA						
	N	n	%	Event Rate	Event Rates	Ratio of Event 95%	Upper Limit of 95%	N	n	%	Event Rate	Event Rates	Ratio of Event 95%	Upper Limit of 95%	N	n	%	Event Rate	Event Rates	Ratio of Event 95%	Upper Limit of 95%
AMENORRHEA **	192	1	1	0.0367	0.886	0.046	52.28	422	2	0	0.0398	0.817	0.059	11.27	284	2	1	0.0689	0.472	0.034	6.515
LEUKORRHEA **	192	0	0	0.0000	UNDF	0.083	UNDF	422	1	0	0.0199	1.634	0.085	96.42	284	0	0	0.0000	UNDF	0.089	UNDF
METRRORRHAGIA **	192	3	2	0.1101	0.295	0.025	2.579	422	4	1	0.0796	0.409	0.037	2.851	284	2	1	0.0689	0.472	0.034	6.515
VAGINITIS **	192	2	1	0.0734	0.443	0.032	6.113	422	3	1	0.0597	0.545	0.045	4.755	284	4	1	0.1378	0.236	0.021	1.648
CERVICITIS **	192	0	0	0.0000	UNDF	0.011	UNDF	422	0	0	0.0000	UNDF	0.021	UNDF	284	0	0	0.0000	UNDF	0.012	UNDF
FEMALE LACTATION **	192	0	0	0.0000	UNDF	0.011	UNDF	422	0	0	0.0000	UNDF	0.021	UNDF	284	0	0	0.0000	UNDF	0.012	UNDF

Event rate is per patient year.

OFC = Olanzapine + Fluoxetine, FLX = Fluoxetine, OLZ = Olanzapine, PLA = Placebo

* Denominator used was for males only, ** = ... females only

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Output is RMP.H6PO.ISS2(POLTESSG)

Treatment Emergent Adverse Events
 Bipolar Depression ISS - Acute Phase
 All Databases and Therapies combined
 Gender-specific events only

Classification Term	FLX						OLZ						PLA								
	N	n	%	Event Rate	Ratio of Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI	N	n	%	Event Rate	Ratio of Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI	N	n	%	Event Rate	Ratio of Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI
FIBROCYSTIC BREAST **	192	0	0	0.0000	UNDF	0.011	UNDF	422	0	0	0.0000	UNDF	0.021	UNDF	284	0	0	0.0000	UNDF	0.012	UNDF
HYPOMENORRHEA **	192	0	0	0.0000	UNDF	0.011	UNDF	422	0	0	0.0000	UNDF	0.021	UNDF	284	0	0	0.0000	UNDF	0.012	UNDF
VAGINAL HEMORRHAGE **	192	1	1	0.0367	0.443	0.006	34.78	422	2	0	0.0398	0.409	0.007	7.848	284	0	0	0.0000	UNDF	0.012	UNDF
PROSTATIC DISORDER *	59	0	0	0.0000	UNDF	UNDF	UNDF	263	1	0	0.0318	0.000	UNDF	48.31	193	0	0	0.0000	UNDF	UNDF	UNDF
TESTIS DISORDER *	59	0	0	0.0000	UNDF	UNDF	UNDF	263	2	1	0.0635	0.000	UNDF	6.595	193	0	0	0.0000	UNDF	UNDF	UNDF

Event rate is per patient year.

OPC = Olanzapine + Fluoxetine, FLX = Fluoxetine, OLZ = Olanzapine, PLA = Placebo

* Denominator used was for males only, ** = ... females only

RMP.H6PSSB.SASPGM(POLTESS) X7690

Output is RMP.H6PO.ISS2(POLTESSG)

Treatment Emergent Adverse Events
 Bipolar Depression ISS - Acute Phase
 All Databases and Therapies combined
 Gender-specific events only

Classification Term	FLX						OLZ						PLA								
	N	n	%	Event Rate	Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI	N	n	%	Event Rate	Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI	N	n	%	Event Rate	Event Rates	Lower Limit of 95% CI	Upper Limit of 95% CI
UNINTENDED PREGNANCY **	192	1	1	0.0367	0.000	UNDF	17.28	422	0	0	0.0000	UNDF	UNDF	UNDF	284	2	1	0.0689	0.000	UNDF	2.514

Event rate is per patient year.

OFC = Olanzapine + Fluoxetine, FLX = Fluoxetine, OLZ = Olanzapine, PLA = Placebo

* Denominator used was for males only, ** = ... females only

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/s/

Doris Bates
12/24/03 10:21:11 AM
CSO

RECEIVED
BY [unclear]

David, Paul A

From: David, Paul A
Sent: Thursday, October 21, 2004 10:32 AM
To: 'Barbara Arning'
Cc: David, Paul A
Subject: Prozac/Cymbalta/Symbyax Medication Guides

Barbara,
Attached is the Medication Guide. This should be submitted in conjunction with the labeling changes requested in our 10/15/04 letter.
Thanks,
Paul

*Paul David, R.Ph., Capt, USPHS
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
ODE1; CDER; FDA
Telephone: 301-594-5530
Fax: 301-594-2859
David@cderr.fda.gov*



SSRI
mguide.doc (351)

-----Original Message-----

From: David, Paul A
Sent: Friday, October 15, 2004 10:47 AM
To: 'Barbara Arning'
Cc: David, Paul A
Subject: Prozac/Cymbalta/Symbyax Supplement Request Letters

Barbara,
As discussed, attached are the supplement request letters for Prozac, Cymbalta, and Symbyax.
Regards,

*Paul David, R.Ph., Capt, USPHS
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
ODE1; CDER; FDA
Telephone: 301-594-5530
Fax: 301-594-2859
David@cderr.fda.gov*

<< File: SYMBYAX LETTER SIGNED 10-15-04.pdf >> << File: PROZAC-SARAFEM LETTER 10-15-04.pdf >> <<
File: CYMBALTA LETTER SIGNED 10-15-04.pdf >>

2 page(s) of draft labeling has been removed from this portion of the review.

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/s/

Paul David
10/22/04 08:00:43 AM
CSO

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