CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Chemistry Review(s)

NDA 21-427

Cymbalta™ (Duloxetine Hydrochloride)

Eli Lilly and Company

Chhagan G. Tele, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-427

2. REVIEW #: 4

3. REVIEW DATE: January 07, 2004

4. REVIEWER: Chhagan G. Tele, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	November 12, 2001
Amendment	February 26, 2002
Amendment	March 12, 2002
Amendment	March 15, 2002
Amendment	March 29, 2002
Amendment	April 4, 2002
Amendment	April 24, 2002
Amendment	June 7, 2002
Amendment	August 19, 2002
Amendment	August 29, 2002
CMC Review #1	September 12, 2002
Request of Type A Meeting	October 31, 2002
Briefing Document	November 15, 2002
Fax	December 19, 2002
Response to Approvable Letter, N(AZ)	March 24, 2003
CMC Review #2	July 7, 2003
Amendment (BZ)	July 30, 2003
CMC Review #3	September 11,2003

CHEMISTRY REVIEW

Chemistry Assessment Section

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BZ)	September 23, 2003
Response to Approvable Letter, N(AZ)	December 23, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Eli Lilly and company
Address:	Lilly Corporate Center, Indianapolis, IN 46285
Representative:	Gregory T. Brophy, Ph.D., director, US Regulatory Affairs
Telephone:	(317) 277-3799

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cymbalta
b) Non-Proprietary Name (USAN): Duloxetine Hydrochloride
c) Code Name/# (ONDC only): LY246916 (LY248686 Hydrochloride)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Major Antidepressant

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20, 30, [redacted] 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

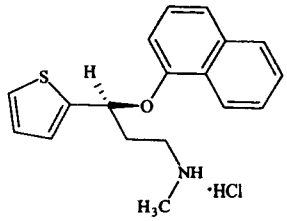
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(+)-(S)-N-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride
Molecular Formula: $C_{18}H_{19}NOS.HCl$
Molecular Weight: 333.88
CAS Number: 136434-34-9
Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	1	Adequate	24-APR-00	Xavier Ysern
	III			1	Adequate	09-AUG-99	Kevin A. Swiss
	III			1	Adequate	26-MAR-01	David T. Lin
	III			1	Adequate	01-SEP-99	James D. Vidra
	III			1	Adequate	02-SEP-99	James D. Vidra
	III			1	Adequate	29-APR-02	Zhei Liang
	III			1	Adequate	14-FEB-02	Rajiv Agarwal
	III			1	Adequate	29-SEP-01	Mike Adams
	III			1	Adequate	29-JUL-99	D. Klein
	III			1	Adequate	20-APR-01	D. Klein

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	—	Commercial IND Indication: — Sponsor: Eli Lilly and Co.
IND	38,838	Commercial IND Indication: Antidepressants Sponsor: Eli Lilly and Co.
IND	—	Commercial IND Indication: — Sponsor: Eli Lilly and Co.
IND	—	Commercial IND Indication: / / Sponsor: Eli Lilly and Co.
NDA	—	Commercial IND Indication: / / Sponsor: Eli Lilly and Co.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	18-JUL-03	
Pharm/Tox	Approvable	11-SEP-02	Linda Fossom, Ph.D.
Biopharm	Acceptable	23-AUG-02	Ron Kavanaugh, Ph.D.
LNC	Acceptable	09-AUG-02	Tia Harper-Velazquez, Pharm.D.
Methods Validation	Pending	18-JUL-03	
DMETS	Acceptable	09-JUL-03	Jinhee Jahng, R.Ph.
EA	Adequate	13-MAR-02	Florian Zielinski, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-427 for Cymbalta™ (duloxetine hydrochloride) is recommended for **APPROVAL** from the Chemistry, Manufacturing and Control standpoint. This recommendation is based on an overall acceptable cGMP recommendation from the Office of Compliance for all manufacturing, packaging, labeling, and testing facilities (see attached EER).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Cymbalta™ (duloxetine hydrochloride) is a delayed release serotonin and norepinephrine reuptake inhibitor (SNRI) for oral administration. It is not related to other SNRIs such as tricyclic, tetracyclic or other available drug products. It is to be marketed as an oral capsule in strengths of 20, 30, 60 mg for the treatment of Major Depressive Disorder (MDD) in adults. [redacted]

The drug substance duloxetine hydrochloride is acid labile. For this reason an encapsulated enteric-coated pellet formulation was selected to protect the drug substance in the stomach. The enteric coating consists of an [redacted] hydroxypropyl methylcellulose acetate succinate. This enteric coating provides stability to the drug substance in the acidic stomach environment for two hours. The finished pellets consist of a sugar sphere core particle, a duloxetine hydrochloride layer, a subcoat layer, an enteric layer and a color layer. The drug product consists of duloxetine hydrochloride enteric coated pellets filled into hard gelatin capsule. Each capsule contains duloxetine hydrochloride equivalent to 20, 30, 60 mg Duloxetine (Delayed Release enteric-coated Pellets). [redacted]

duloxetine hydrochloride to deliver duloxetine equivalent of 20, 30, 60 mg. The capsules also contain sucrose and hydroxypropyl methylcellulose talc hydroxypropyl methylcellulose acetate succinate as enteric coating polymer, triethyl

citrate [ ] The capsule colors are distinct for each strength and are noted in the Component/Composition section of Chemistry Review #1 and how supplied section of the Package Insert. The capsule colors are 20 mg (opaque green, opaque green), 30 mg (opaque blue, opaque white), [ ] 60 mg (opaque blue, opaque green). The capsules are imprinted with edible ink. Each strength of Cymbalta™ is packaged in bottles containing 30, 60, 180, or 1000-count dosage units per [ ]

The drug substance, duloxetine hydrochloride is a new molecular entity with one chiral center. Duloxetine hydrochloride is a white to slightly brownish white solid.

Duloxetine hydrochloride is not hygroscopic and is slightly soluble in water. All the batches of duloxetine hydrochloride presented in the original NDA were manufactured at the Eli Lilly Tippecanoe, Indiana site (CFN # 1813682). Lilly has updated the drug substance specifications by lowering the specifications of [ ]

B. Description of How the Drug Product is Intended to be Used

Cymbalta™ is to be marketed in strengths of 20 mg, 30 mg, and 60 mg as 14, 30, 60, 90, 180 or 1000-counts in white high density polyethylene (WHDPE) bottles. In addition, Cymbalta™ capsules, 30 mg and 60 mg will be supplied in a 7-count dosage unit bottle. The bottles will be sealed with closures containing an aluminum foil [ ] liner. A plastic child-resistant closure (CRC) will be used for those bottles to be dispensed directly to the consumer. Alternatively, the Cymbalta™ capsules may be packaged in [ ] blister [ ] The capsules are packaged with one capsule per blister cavity. The recommended starting dose is 60 mg/day, on either once or twice daily schedule, without regard to meals. Efficacy and safety in major depressive disorder were demonstrated in a dose range of 40 to mg/day in

clinical trials. However, dose above 60 mg/day were not demonstrated to be more efficacious than the 60 mg/day dose.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-427 for Cymbalta™ (duloxetine hydrochloride) is recommended for **APPROVAL** from the Chemistry, Manufacturing and Control standpoint. This recommendation is based on an overall acceptable cGMP recommendation from the Office of Compliance for all manufacturing, packaging, labeling, and testing facilities (see attached EER).

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Reviewer:	Chhagan Tele, Ph.D.
Chemistry Team Leader:	Thomas Oliver, Ph.D.
Project Manager:	Doris Bates, R.Ph.

D. CC Block

Orig. NDA 21-427
HFD-120/Divison File
HFD-120/DBates
HFD-120/CTele
HFD-120/TOliver

Redacted 4

page(s) of trade secret and/or confidential commercial information (b4)

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

/s/

Chhagan Tele
1/7/04 03:20:26 PM
CHEMIST

Thomas Oliver
1/7/04 03:28:35 PM
CHEMIST