# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# NDA 21-427

## Chemistry Review(s) - #2

#3

CHEMISTRY REVIEW

# 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**

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# Chemistry Review Data Sheet

1. NDA 21-427

2. REVIEW #: 3

3. REVIEW DATE: September 11, 2003

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, 2001 |
| CMC Review #2 | September 11, 2003 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Request of Type A Meeting | October 31, 2002 |
| Briefing Document | November 15, 2002 |
| Fax | December 19, 2202 |
| Response to Approvable Letter, N(BZ) | March 24, 2003 |

Chemistry Review Data Sheet

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

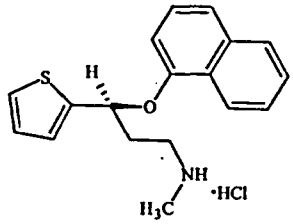
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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 |
|---|---|---|---|---|---|---|---|
| | III | | | 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

Chemistry Review Data Sheet

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<br>Indication: ✓<br>Sponsor: Eli Lilly and Co. |
| IND | 38,838 | Commercial IND<br>Indication: Antidepressants<br>Sponsor: Eli Lilly and Co. |
| IND | — | Commercial IND<br>Indication: ✓<br>Sponsor: Eli Lilly and Co. |
| IND | — | Commercial IND<br>Indication: ✓<br>Sponsor: Eli Lilly and Co. |
| NDA | — | Commercial IND<br>Indication: ✓<br>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 **NOT APPROVABLE** from the Chemistry, Manufacturing and Control standpoint because the Office of Compliance has recommended a **WITHHOLD**. This recommendation is based on significant cGMP violations at the finished product manufacturing facility Eli Lilly and Co., Indianapolis (CFN 1819470) (see attached EER). The approval, however, is based on an overall acceptable cGMP recommendation from the Office of Compliance for all manufacturing, packaging, labeling, and testing facilities.

### 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. 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 — _ of hydroxypropyl methylcellulose acetate succinate. This enteric coating provides stability to the drug substance in the acidic stomach environment for 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). ⊏

] ' 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, [redacted] 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), [redacted] and 60 mg (opaque blue, opaque green). The capsules are imprinted with edible ink. Each strength of Cymbalta™ is packaged in bottles containing [redacted] 30, 60, 180, or 1000-count dosage units per [redacted]

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

[redacted] 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 [redacted]

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

Cymbalta™ is to be marketed in strengths of 20 mg, 30 mg, 40 mg, and 60 mg as [redacted] 30, 60, 90, 180 or 1000-counts [redacted] 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 [redacted] 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 [redacted] blister [redacted] 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 [redacted] 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 **NOT APPROVABLE** from the Chemistry, Manufacturing and Control standpoint because the Office of Compliance has recommended a **WITHHOLD**. This recommendation is based on significant cGMP violations at the finished product manufacturing facility Eli Lilly and Co., Indianapolis (CFN 1819470) (see attached EER). The approval, however, is based on an overall acceptable cGMP recommendation from the Office of Compliance for all manufacturing, packaging, labeling, and testing facilities.

- All other CMC concerns related to the drug substance and drug product sections as outlined in the Chemistry review #1 by Dr. Christy John have been addressed in review #2.

## 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** 2

**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/
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Chhagan Tele
9/12/03 09:28:04 AM
CHEMIST

Thomas Oliver
9/12/03 11:13:05 AM
CHEMIST

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

## NDA 21-427

# Chemistry Review(s) - #3

#2

CHEMISTRY REVIEW

# 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**

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C. Basis for Approvability or Not-Approval RecommendationError! Bookmark not defined.

III. Administrative.....9

A. Reviewer's Signature.....8

B. Endorsement Block.....9

C. CC Block.....9

Chemistry Assessment.....10

# Chemistry Review Data Sheet

1. NDA 21-427

2. REVIEW #: 2

3. REVIEW DATE: June 04, 2003

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, 2001 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Request of Type A Meeting | October 31, 2002 |
| Briefing Document | November 15, 2002 |
| Fax | December 19, 2202 |
| Response to Approvable Letter, N(BZ) | March 24, 2003 |

Chemistry Review Data Sheet

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] and 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

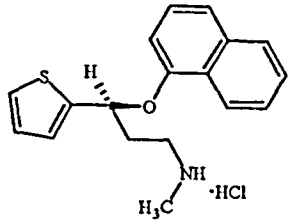
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____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 |
|---|---|---|---|---|---|---|---|
| — | III | | | 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:
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Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

Chemistry Review Data Sheet

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<br>Indication: —<br>Sponsor: Eli Lilly and Co. |
| IND | 38,838 | Commercial IND<br>Indication: Antidepressants<br>Sponsor: Eli Lilly and Co. |
| IND | — | Commercial IND<br>Indication: —<br>Sponsor: Eli Lilly and Co. |
| IND | — | Commercial IND<br>Indication: —<br>Sponsor: Eli Lilly and Co. |
| NDA | — | Commercial IND<br>Indication: —<br>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 **APPROVABLE** from the CMC stand point. The approval, however, is based on an overall acceptable cGMP recommendation from FDA 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. 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 [ ] of 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). [ ] 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), [ ] and 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 [ ] bottles. [ ]

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, 40 mg, and 60 mg as 30, 60, 90, 180 or 1000-counts in [ ] 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 APPROVABLE from the CMC stand point based on the following:

- An acceptable recommendation from the FDA's Office of Compliance regarding cGMP status of all drug substance and drug product manufacturing, release, stability testing and packaging sites is still needed.

- All CMC concerns related to the drug substance and drug product sections as outlined in the Chemistry review #1 by Dr. Christy John have been addressed in this review (#2).

## III. Administrative

### A. Reviewer's Signature

### 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

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

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/s/

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Chhagan Tele
7/18/03 04:10:30 PM
CHEMIST

Thomas Oliver
7/18/03 04:20:19 PM
CHEMIST

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

## NDA 21-427

# Chemistry Review(s) - #4

# NDA 21-427

## CYMBALTA (DULOXETINE HYDROCHLORIDE)

## ELI LILLY AND COMPANY

**CHRISTY S. JOHN, Ph.D.**

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**

**HFD-120**

## Review of Chemistry, Manufacturing, and Controls

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# Chemistry Review Data Sheet

1. NDA 21-427

2. REVIEW #: 1

3. REVIEW DATE: September 12, 2002

4. REVIEWER: Christy S. John, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| IND # 38,838 | March 5, 1992 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | November 12, 2001 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Eli Lilly and Company |
| Address: | Eli Lilly Corporate Center, Indianapolis, IN 46285 |
| Representative: | Gregory T. Brophy, Ph.D. |

Telephone: (317)277-3799

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cymbalta
b) Non-Proprietary Name/ USAN[1992]: 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 mg, 30 mg, and 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

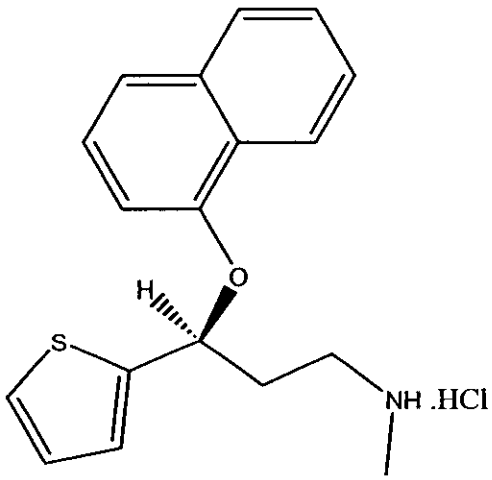
CA NAME: (+)-(S)-N-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride

MOLECULAR FORMULA: $C_{18}H_{19}NOS.HCl$

MOLECULAR WEIGHT: 333.88

CHEMICAL ABSTRACT SERVICE NUMBER: 136434-34-9

STRUCTURAL FORMULA:




17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | REVIEWED BY |
|---|---|---|---|---|---|---|---|
| [illegible] | | [illegible] | | 1 | Adequate | 04/24/2000 | Xavier Ysern |
| [illegible] | | [illegible] | [illegible] | | Adequate | 08/09/1999 | Kevin A. Swiss |
| [illegible] | | [illegible] | | 1 | Adequate | 03/26/2001 | David T. Lin |

| | | | | | | |
|---|---|---|---|---|---|---|
| [redacted] | | | 1 | Adequate | 09/01/1999 | James D. Vidra |
| [redacted] | | | 1 | Adequate | 09/02/1999 | James D. Vidra |
| [redacted] | | | 1 | Adequate | 04/29/2002 | Zhei Liang |
| [redacted] | | | 1 | Adequate | 02/14/2002 | Rajiv Agarwal |
| [redacted] | | | 1 | Adequate | 09/29/2001 | Mike Adams |
| [redacted] | | | 1 | Adequate | 07/29/99 | D. Klein |
| [redacted] | | | 3 | Adequate | 04/20/2001 | 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: N/A**

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Pending | | |
| Pharm/Tox | Approvable | 11-SEP-02 | Linda Fossom, Ph.D. |
| Biopharm | Acceptable | 23-AUG-02 | Ron Kavanaugh, Ph.D. |
| DMETS | Acceptable | 09-AUG-02 | Tia Harper-Velazquez, Pharm.D. |
| Methods Validation | Pending | | |
| EA | Adequate | 13-MAR-02 | Florian Zielinski, Ph.D. |
| Microbiology | | | |

# 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 Approvable from the Chemistry, Manufacturing and Controls standpoint. This approval, however, is contingent on an acceptable cGMP recommendation from FDA Office of Compliance for all manufacturing, packaging, and testing sites and satisfactory responses to the CMC deficiencies (drug substance and drug product) outlined in this review.

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

N/A

## 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. The 'pharmacologically active' drug substance (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride has one chiral center. It is a new molecular entity. Duloxetine hydrochloride is a white to light brown powder and is slightly soluble in water.

[ ] is defined as a starting material. According to a teleconference (held on September 28, 2001 for IND 38,338) minutes, Dr. Lostritto and Dr. Patel of the Agency accepted the designation of [ ] as a starting material. This reviewer was not present at this meeting. However, this reviewer disagrees with the designation of [ ] as starting material because it does not appear to meet the definition of a starting material set out in the *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (1987).*

The drug substance will be manufactured at Lilly's site in Indianapolis, IN. The drug substance is very well characterized using [ ] analytical methods. The drug substance has also been shown to be [ ] for extended periods of time. However, the drug substance [ ] testing. The drug substance duloxetine hydrochloride is acid labile. In order to protect the drug substance in the stomach, an

enteric coated drug product was developed. The enteric coating consists of an of hydroxypropyl methylcellulose acetate succinate. This enteric coating provides stability to the drug substance in the acidic stomach environment for two hours. For this reason the product is labeled as "delayed release". The drug product consists of duloxetine hydrochloride enteric-coated pellets filled into hard gelatin capsules. The finished pellets consist of a sugar sphere core particle, a duloxetine hydrochloride layer, a subcoat layer, an enteric layer and a color layer. A coating process is used to apply the four layers.

Each capsule contains enteric-coated pellets of duloxetine hydrochloride equivalent to 20 mg, 30 mg, or 60 mg of duloxetine. Inactive ingredients include FD&C Blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 mg capsules also contains iron oxide yellow.

Duloxetine hydrochloride in the drug product formulation

with hydroxypropyl methyl cellulose acetate succinate (HPMCAS), the enteric coating polymer.

. The sponsor will be asked to provide the manufacturing details and specifications for HPMCAS to help address this issue. In addition, the sponsor will be requested to submit updated drug product stability data.

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

Duloxetine hydrochloride Capsules, 20 mg, 30 mg, — and 60 mg may be supplied in bottles containing — 30, 60, 90, 180 or 1000-count dosage units per bottle. In addition, Duloxetine Capsules, 30 mg, and 60 mg will be supplied in a 7-count dosage unit bottle. Duloxetine capsules will be [ ] bottles. 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. [ ] closures will be used on those bottles intended to be repackaged or for use within institutions such as hospitals and nursing homes.
Alternatively, the duloxetine capsules may be packaged in — blister that are sealed with [ ]. The capsules are packaged with one capsule per blister cavity.

**C. Basis for Approvability or No-Approval Recommendation**:

NDA 21-427 for Cymbalta (duloxetine hydrochloride) is recommended "Approvable" from CMC standpoint based on the following:

A) Pending recommendation from Office of Compliance, FDA regarding cGMP status of manufacturing, controls and packaging facilities for the drug substance and drug product.

The Lilly Indiana site (CFN 1819470, drug product manufacturer, labeler, and packager) is highlighted "RED" in EES and is currently coded as OAI ALERT. Please see a copy of scanned OC report at the end of the review. If the Office of Compliance (OC) recommends an overall withold recommendation for this NDA, the CMC recommendation will change from Approvable to **Not Approvable**. There are no other facilities submitted in the NDA that perform these functions.

B) CMC concerns related to the drug substance and drug product sections as outlined in the review. The deficiencies are detailed in the draft deficiency letter at the end of this review to be conveyed to Eli Lilly.

## III. Administrative

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

**C. CC Block**

**Redacted** 99

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