# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-520**

## CHEMISTRY REVIEW(S)

# NDA 21-520

## Symbyax
## (Olanzapine/Fluoxetine HCl Combination Capsules)

**Eli Lilly and Company**

**Li-Shan Hsieh, Ph. D.**
**Review Chemist of HFD-150**
**Division of Oncology Drug Products**

**For**

**HFD-120**
**Division of Neuropharmacological Drug Products**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA # 21-520

2. REVIEW #: 2

3. REVIEW DATE: 10-Sep-2003

4. REVIEWER: Li-Shan Hsieh, Ph. D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | | Document Date |
|---|---|---|
| End of phase II CMC discussion for IND 28,705 | | 31-Aug-2000 |
| Pre-NDA meeting | | 29-Aug-2001 |
| Original | | 04-Nov-2002 |
| N(BC) | CMC Information | 27-Jan-2003 |
| N(BL) | Revised container labeling artwork, all strengths and package | 27-Feb-2003 |
| N(BM) | SYMBYAX® new trade name request | 11-Apr-2003 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | | Document Date |
|---|---|---|
| N(AZ) | CMC responses | 24-June-2003 |

7. NAME & ADDRESS OF APPLICANT:

Name: Eli Lilly and Company

Address: Lilly Corporate Center
Indianapolis, IN 46285

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Representative: Gregory T. Brophy, Ph. D.
Director, US Regulatory Affairs

Telephone: 317-277-3799

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Symbyax™
b) Non-Proprietary Name (USAN): Olanzapine/Fluoxetine Combination
c) Code Name/# (ONDC only): LY170053 or LY900000 (Lilly code), olanzapine/fluoxetine hydrochloride, OFC
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

Olanzapine and fluoxetine HCl drug substances were approved for the marketed Zyprexa® (olanzapine) tablets and Prozac® (fluoxetine HCl) capsules, tablets and oral solution.

Olanzapine formulation is marketed for the following:

| | |
|---|---|
| NDA 20-592 | Zyprexa® Tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg. |
| NDA 20-592 | Zyprexa® Zydis (orally disintegrating Tablets), 5 mg, 10mg, 15mg, and 20 mg |

Fluoxetine HCl formulations are marketed for the following:

| | |
|---|---|
| NDA 18-936 | Prozac® Pulvules, 10 mg, 20 mg, 40 mg, and 60 mg, Approved 29-Dec-87 |
| NDA 18-936 | Sarafem Pulvules, 10 and 20 mg, |
| NDA 20-101 | Prozac® Oral solution MS5120, 20 mg/5 mL, Approved 24-Apr-91 |
| NDA 20-974 | Prozac® Tablets, 10 mg and 20 mg, Approved 9-Mar-99 |

10. PHARMACOL. CATEGORY:
Depressive Episodes Associated with Bipolar Disorder

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: Olanzapine/ Fluoxetine mg ——, 6/25, 12/25, 6/50, 12/50

13. ROUTE OF ADMINISTRATION: oral

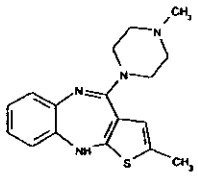
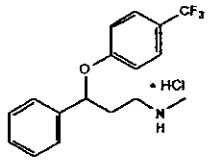
14. Rx/OTC DISPENSED: _xx_ Rx ___ OTC

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

_____SPOTS product – Form Completed

__xx__Not a SPOTS product

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

| **Olanzapine** | **Fluoxetine** |
|---|---|
| USAN:<br>2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b][1,5]benzodiazepine<br>or<br>10*H*-thieno[2,3-b][1,5]benzodiaepine,2-methyl-4-(4-methyl-1-piperazyl)-<br><br>INN: Olanzapine.<br><br>Lilly Compound #: LY170053<br><br>CAS #: 132539-06-1 | USAN:<br>Benzenpropanamine, N-methyl-γ- [4-(trifluoromethyl)phenoxy]-, (±)hydochloride<br>or<br>(±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-totyl]propylamine hydrochloride<br><br>Non-proprietary Name (USAN):<br>Fluoxetine Hydrochloride, USP<br><br>Lilly Compound #: LY110140 |
| Empirical Formula: $C_{17}H_{20}N_4S$<br>Molecular Weight: 312.44<br>Structure:<br>  | Molecular Formula: $C_{17}H_{18}F_3NO \cdot HCl$<br>Molecular Weight: 345.79<br>Structure:<br>  |

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | III | [redacted] | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Evista N20-815 |
| [redacted] | III | [redacted] | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Evista N20-815 |
| [redacted] | III | [redacted] | | 4 | Adequate | CMC review #1 | Approval for |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | (15-Apr-03) | Evista N20-815 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Evista N20-815 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Zyprexa N20-592 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Prozac N 18-936 and Darvocet N 17-122 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Prozac N18-936 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Zyprexa N20-592 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | Approval for Zyprexa N20-592 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | Comply with 21 CFR 210, 211 |
| | III | | | 4 | Adequate | CMC review #1 (15-Apr-03) | |
| | IV | | | 3 | Adequate for BSE concern | 30-Aug-2001 | Dr. Raymond Frankewich |
| | IV | | | 4 | Adequate for BSE concern | CMC review #1 (15-Apr-03) | / are provided. |

[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 |
|---|---|---|
| NDA | 20-4592 /Y-006 | CMC information of drug substance Olanzapine |
| NDA | 18-936 /Y- 104 | CMC information of drug fluoxetine |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Withhold | 04-Dec-2002 | Melvin Robinson |
| EES | Acceptable | 28-Jul-2003 | Janine M. D'Ambrogio |
| Pharm/Tox | Pending | | Sonia Tabacova, Ph. D |
| Biopharm | Approvable | 04-Mar-2003 | Sally Usdin Yasuda, MS, Pharm. D. |
| Methods Validation | Acceptable | 14-Apr-2003 | Li-Shan Hsieh, Ph.D. |
| DMETS | Pending | | |
| EA | Categorical exclusion granted | 14-Apr-2003 | Li-Shan Hsieh, Ph. D. |

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for NDA 21-520

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

All chemistry deficiencies identified in review #1 have been corrected. Compliance provided an overall acceptable recommendation on 28-Jul-2003 for all submitted sites. Therefore, this NDA is recommended for **approval.**

### 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)

The formulations for Olanzapine/Fluoxetine Combination Capsules, —, 6/25, 12/25, 6/50, and 12/50 (mg olanzapine/mg fluoxetine base) contain pregelatinized starch as a diluent and dimethicone as a lubricant. The —, 6/25, and 12/25 mg capsules, which are filled into Size 3 empty gelatin capsules, differ only in the amount of olanzapine and pregelatinized starch in the formulation. The 6/50 and 12/50 mg capsules, which are filled into Size 2 empty gelatin capsules, differ only in the amount of olanzapine and pregelatinized starch in the formulation. All strengths are differentiated by capsule shell color and identification (strength) imprint. The 6/50 and 12/50 mg strengths have a higher fill weight and are also differentiated by a larger capsule size. In this submission,

Olanzapine is a psychotropic agent that belongs to the thienobenzodiazepine class and is a selective monoaminergic antagonist with high affinity binding to serotonin $5HT_{2A/2C}$, dopamine $D_{1-4}$, muscarinic $M_{1-5}$, histamine $H_1$ and adrenergic (alpha) receptors. Olanzapine is a yellow crystalline solid, which is practically insoluble in water. Previous experience suggests that olanzapine is moisture sensitive; therefore, moisture protective packaging was selected.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI) and was initially developed and marketed as an antidepressant (Prozac®, fluoxetine hydrochloride). Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Both olanzapine and fluoxetine HCl are well-characterized drug substances approved and marketed in various countries in single entity oral formulations. Oral olanzapine formulations are marketed as coated tablets (Zyprexa® Tablets NDA 20-592) and oral lyophilizates (NDA 21-086). Oral fluoxetine HCl formulations are marketed as capsules (Prozac® Pulvules NDA 18-936), tablets (Prozac® Tablets NDA 20-974), and as an oral solution (Prozac® Oral solution NDA 20-101).

Although previously **amber** HDPE bottles were used for Zyprexa Tablets and Prozac Capsules, the use of **white** HDPE bottles for Olanzapine/Fluoxetine Combination Capsules showed no significant impact by light. Similar to Zyprexa Tablets, Olanzapine/Fluoxetine Combination Capsules have been packaged in [redacted] Aluminum Foil Blisters. In addition, all bottle presentations are sealed with [redacted] and contain [redacted] canisters filled with [redacted] for moisture absorption.

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

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder. Proposed administration includes once daily in the evening, without regard to meals, generally beginning with the 6/25-mg capsule. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. The recommended storage statement is: Store of 25 °C (77 °F); excursions permitted to 15° – 30° C ( 59° – 86° F) [see USP Controlled Room Temperature]. Keep tightly closed and protect from moisture. The approved shelf-life is 24 months.

**C. Basis for Approvability or Not-Approval Recommendation**

NDA 21-520 is recommended Approval from CMC standpoint based on the following:

(1) The Eli Lilly site [redacted] has been **withdrawn**. All facilities involved in the manufacture and control of the drug substance and drug product were found acceptable by the Office of Compliance on 28-Jul-2003.

(2) All incorrectly listed excipients in the package insert have been revised.

## III. Administrative

| | |
|---|---|
| Chemistry Reviewer: | Li-Shan Hsieh, Ph. D. |
| Chemistry Team Leader: | Thomas Oliver, Ph. D. |
| Project Manager: | Doris Bates, Ph. D. |

8 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable

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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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Li-Shan Hsieh
9/10/03 01:56:20 PM
CHEMIST

Thomas Oliver
9/10/03 02:15:04 PM
CHEMIST