CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-235

CHEMISTRY REVIEW(S)

OCT 12 2000

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21,235 **DATE REVIEWED:** 12-OCT-2000 **REVIEW #:** 2

REVIEWER: Robert H. Seevers, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE ASSIGNED DATE
N-BC	06-SEP-2000	11-SEP-2000 15-SEP-2000

NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME
Proprietary: Fluoxetine HCl
Established: Prozac® ————
Code Name/#: N/A
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: Depression

DOSAGE FORM: Capsule Delayed Release with green cap and clear body imprinted with 'Lilly' on the green cap and '3004' and '90 mg' on clear body in black ink. Printing is horizontal to the capsule.

STRENGTHS:	90 mg			
ROUTE OF ADMINISTRATION:	Oral			
R_x /OTC	X	**R_x**		**OTC**
SPECIAL PRODUCTS:		**Yes**	X	**No**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
CA Name: Benzenepropanamine, N-methyl-g-[4-(trifluoromethyl)-phenoxyl]-, hydrochloride
USAN Name: Fluoxetine Hydrochloride
Chemical Formula: $C_{17}H_{18}NOF_3 \cdot HCl$
Molecular Weight: 345.79
CAS registry #: 59333-67-4
Structure: see USP

CONSULTS
EES returned an overall ACCEPTABLE recommendation on September 27, 2000.

CONCLUSIONS & RECOMMENDATIONS:
The sponsor has responded adequately to the issues raised in the Agency's August 3, 2000

chemistry discipline review letter. With the ACCEPTABLE recommendation for the manufacturing sites, this NDA may be APPROVED from a CMC standpoint. There are two comments that will be sent in a discipline review letter to the sponsor; see draft letter.

[/S/]
Robert H. Seevers, Chemistry Team Leader

10/12/00
Date

cc:
Org. NDA 21-235
HFD-120/Division File
HFD-120/GGill-Sangha
HFD-120/ RSeevers
HFD-120/PDavid
HFD-810/HPatel
HFD-810/Jsimmons

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ON ORIGINAL

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JUL 3 2000

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21,235 **DATE REVIEWED:** 30-Jun-2000 **REVIEW #:** 1

REVIEWER: Gurpreet Gill-Sangha, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original (presubmission)	13-Feb-2000	15-Feb-2000	25-Feb-2000
Original	13-Mar-2000	14-Mar-2000	21-Mar-2000
N(BC) Amendment	16-Mar-2000	21-Mar-2000	28-Mar-2000
N(BC) Amendment	24-Mar-2000	27-Mar-2000	29-Mar-2000
N(BC) Amendment	28-Mar-2000	29-Mar-2000	6-Apr-2000
N(BC) Amendment	13-Apr-2000	14-Apr-2000	25-Apr-2000
N(BC) Amendment	1-May-2000	5-May-2000	12-May-2000
N(BC) Amendment	18-May-2000	23-May-2000	25-May-2000
N(BB) Amendment	22-May-2000	23-May-2000	25-May-2000

NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME

Proprietary:	Fluoxetine HCl
Established:	Prozac®;
Code Name/#:	N/A
Chem.Type/Ther.Class:	3S

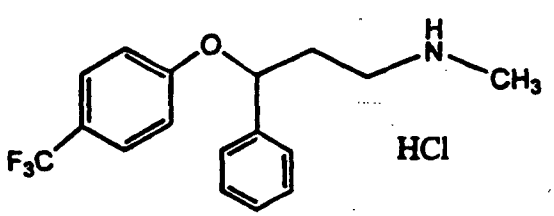
PHARMACOL. CATEGORY/INDICATION: Depression

DOSAGE FORM: Capsule Delayed Release with green cap and clear body imprinted with 'Lilly' on the green cap and '3004' and '90 mg' on clear body in black ink. Printing is horizontal to the capsule.

STRENGTHS: 90 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC X Rx ___ OTC
SPECIAL PRODUCTS: ___ Yes X N

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

CA Name: Benzenepropanamine, N-methyl-γ-[4-(trifluoromethyl)-phenoxyl]-, hydrochloride
USAN Name: Fluoxetine Hydrocholride
Chemical Formula: $C_{17}H_{18}NOF_3$ .HCl
Molecular Weight: 345.79
CAS registry #: 59333-67-4
Structure:



SUPPORTING DOCUMENTS:

Type/No.	Subject	Holder/ LOA	Pg./ Vol. in NDA	Status	Review and Letter Date
I53,079	Flouxetine Hydrocholoride weekly dosing capsules	Eli Lilly	-	Active as of 5/11/97	N/A
N18-936	Flouxetine Hydrochloride; Prozac® Pulvules	Eli Lilly	-	Approved on 12/29/87	N/A
[redacted]			Vol. 1.1, page 102	Adequate	Reviewed by Gurpreet Gill-Sangha, Ph.D. on 6/22/00
			Vol. 1.1, page 104	Adequate	Reviewed by Gurpreet Gill-Sangha, Ph.D. on 4/3/00
			Vol. 1.1, page 110	Adequate	Reviewed by Gurpreet Gill-Sangha, Ph.D. on 3/10/00
			Vol. 1.1, page 110	Adequate	Reviewed by Don Klein. Ph.D. on 7/29/99
			Vol. 1.1, page 178	Adequate	Reviewed by Sherita McLamore, Ph.D. on 3/3/00
			Vol. 1.1, page 179	Adequate	Reviewed by Gurpreet Gill-Sangha, Ph.D. on 4/14/00
			Vol. 1.1, page 180	DMF not reviewed since [redacted] not included in stability protocol for Prozac® [redacted]	
			Vol. 1.1, page 181	Adequate based on the combination of two reviews	Reviewed by Ravi S. Harapanhalli, Ph.D. for all [redacted] bottles on 5/4/99 and reviewed by Rajendra Uppoor, Ph.D. for quality controls and manufacturing of holder on 8/25/98

Type/No.	Subject	Holder/ LOA	Pg./ Vol. In NDA	Status	Review and Letter Date
[			Vol. 1.1, page 182	Adequate	Reviewed by Stuart Zimmerman, Ph.D. on 1/17/96
			Vol. 1.1, page 183	Adequate	Reviewed by James D. Vidra, Ph.D. on 9/01/99
			N(BC) 3/16/00 page2	Adequate	Reviewed by James D. Vidra, Ph.D. on 9/01/99
			Vol. 1.1, page 185 and N(BC) 3/28/00, pages 1-3	**Inadequate for the holder** ***Adequate for NDA 21-235 based on the information provided by Eli Lilly with USP testing results in their amendment dated 3/28/00 for bottles and bottle with insert. The information provided by Lilly results in an adequate use of ——— bottles from ——— for NDA 21-235. In addition ——— used for manufacture of the bottles and inserts are adequate as per DMF*** ———	
[			Vol. 1.1, page 186 and 187	Adequate for both resins	5502BN reviewed by Su C. Tso, Ph.D. on 12/15/99 55180 reviewed by Gurpreet Gill-Sangha, Ph.D. on 4/14/00
			Vol. 1.1, page 188	Adequate	Reviewed by Sue-Ching Lin on 8/02/99
			Vol. 1.1, page 189	**Inadequate**	Reviewed by Gurpreet Gill-Sangha, Ph.D. on 6/20/00
			Vol. 1.1, page 190	Adequate	Reviewed by M. J. Sloan, Ph.D. on 9/16/99
			Vol. 1.1, page 191	Adequate	Reviewed by Joseph T. Piechocki, Ph.D. on 8/11/99
			Vol. 1.1, page 169-76	Adequate	Reviewed by Thomas A. Broadbent, Ph.D. on July 10, 1998

RELATED DOCUMENTS (if applicable):

1. NDA 20-974: Flouxetine Hydrocholoride tablets(10 and 20 mg), Approved on 3/9/99
2. NDA 18-936: Flouxetine Hydrocholoride Pulvules, Approved on 12/29/87
3. NDA 20-101: Flouxetine Hydrocholoride oral solution, Approved on 4/24/91
4. NDA 20-187: Flouxetine Hydrocholoride for obsessive compulsive disorder, Approved on 2/28/94
5. [redacted]

OTHER REQUESTS: Establishment evaluation requests were sent out as listed below:

Site CFN#	Site Location	Site Function	Submitted to OC	Status
[redacted]			March 16, 2000	Pending
1813682	Eli Lilly	DS manufacture	March 16, 2000	Pending
1819470	Eli Lilly	DS manufacture	March 16, 2000	Pending
1819470	Eli Lilly	DP manufacture and packaging	March 20, 2000	Pending
[redacted]			March 16, 2000	Pending
			March 16, 2000	Pending
			March 16, 2000	Pending
			March 16, 2000	Pending
			March 23, 2000	Pending
			March 23, 2000	Pending

REMARKS:

1. NDA 18-936 is referenced for the drug substance fluoxetine hydrochloride, USP.
2. The following CMC sections of the NDA are acceptable:

- Drug Substance,
- Drug Product Components and Composition,
- Specifications and Methods for Drug Product Ingredients,
- Drug Product Manufacturer,
- Environmental Assessment,
- Investigational Formulations and
- Labeling.

3. The following sections in the Drug product section of the NDA need further clarifications (see draft letter for specifics):

- Methods of Manufacturing and Packaging,
- Regulatory Specifications and Methods,
- Methods Validation,
- Container Closure system,
- Drug Product Stability, and
- Establishment Inspection (pending OC recommendation).

CONCLUSIONS & RECOMMENDATIONS:

NDA 21-235 is recommended **Approvable** based on CMC section. The approvability is contingent on pending evaluation of manufacturing sites by the district offices (refer to EES for results) and adequate responses from the sponsor to the questions addressed in the draft letter. The Prozac® ——— provides acceptable stability data for 24 month expiry period in specific container closures on the stability protocol (see draft letter for details on the approvable container closures).

[/S/] 6/30/00 [/S/] 9/3/00

Gurpreet Gill-Sangha, Ph.D. Date Robert H. Seevers, Ph.D. Date
Review Chemist, HFD-120 Chemistry Team Leader

cc:
Org. NDA 21-235
HFD-120/Division File
HFD-120/GGill-Sangha
HFD-120/ RSeevers
HFD-120/PDavid
HFD-810/HPatel
HFD-810/JSimmons
Filename: C:\data\My Documents\data gill\Nda\21235\rev1.doc

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P. Davis

AUG 3 - 2000

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21,235 **DATE REVIEWED: 1-Aug-2000** **REVIEW #: 2** AUG - 3 2000

REVIEWER: Gurpreet Gill-Sangha, Ph.D.

Submission type	Document date	CDER date	Received by chemist
N(BC) Amendment	19-July-2000	25-July-2000	18-July-2000 by e-mail 28-July-2000 paper copy

NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME

Proprietary:	Fluoxetine HCl
Established:	Prozac®
Code Name/#:	N/A
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: Depression

DOSAGE FORM: Capsule Delayed Release with green cap and clear body imprinted with 'Lilly' on the green cap and '3004' and '90 mg' on clear body in black ink. Printing is horizontal to the capsule.

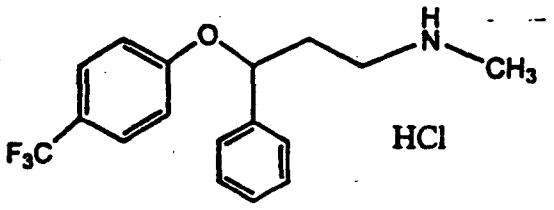
STRENGTHS: 90 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC	X	Rx		OTC
SPECIAL PRODUCTS:		Yes	X	N

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

CA Name: Benzenepropanamine, N-methyl-γ-[4-(trifluoromethyl)-phenoxyl]-, hydrochloride
USAN Name: Fluoxetine Hydrocholride
Chemical Formula: $C_{17}H_{18}NOF_3$ .HCl
Molecular Weight: 345.79
CAS registry #: 59333-67-4
Structure:



SUPPORTING DOCUMENTS: None

CONCLUSIONS & RECOMMENDATIONS:

NDA 21-235 is recommended **Approvable** based on CMC section. The approvability is contingent on pending evaluation of manufacturing sites by the district offices (refer to EES for results) and adequate responses from the sponsor to the questions addressed in the draft letter.

[/S/] 8/1/00 [/S/] 8/3/00

Gurpreet Gill-Sangha, Ph.D. Date Robert H. Seevers, Ph.D. Date
Review Chemist, HFD-120 Chemistry Team Leader

cc:
Org. NDA 21-235
HFD-120/Division File
HFD-120/GGill-Sangha
HFD-120/ RSeevers
HFD-120/PDavid
HFD-810/HPatel
HFD-810/JSimmons
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