CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020974

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-974 **CHEM REVIEW: #1** **REVIEW DATE: 1/19/99**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3/19/98	3/20/98	3/25/98
N(BC) Amendment	6/5/98	6/8/98	6/19/98
N(BC) Amendment	7/7/98	7/8/98	7/8/98
N(BC) Amendment	7/30/98	7/31/98	8/6/98
N(BC) Amendment	8/4/98	8/5/98	8/10/98
N(BC) Amendment	8/24/98	8/25/98	9/1/98
N(BC) Amendment	8/26/98	8/27/98	9/1/98
N(BC) Amendment	9/21/98	9/22/98	9/29/98
N(BC) Amendment	9/29/98	9/30/98	10/1/98
N(BC) Amendment	11/20/98	11/23/98	12/2/98

NAME AND ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:

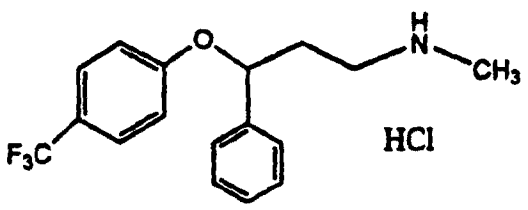
Proprietary:	Prozac® Tablets
Non proprietary/USAN:	Fluoxetine hydrochloride
Code Name/Number:	None
Chem. Type/Ther. Class:	1S

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM:	**10mg:** green, elliptical shape, coated tablet, scored. **20mg:** yellow, round shape, coated tablet.
STRENGTHS:	10mg and 20mg
ROUTE OP ADMINISTRATION:	Oral
DISPENSED:	xx RX ___OTC
SPECIAL PRODUCTS:	__Yes xx No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

CA Name: Benzenepropanamine, N-methyl-γ-[4-(trifluormethyl)-phenoxy]-, hydrochloride
USAN Name: Fluoxetine Hydrochloride
Chemical Formula: $C_{17}H_{18}NOF_3$ .HCl
Molecular Weight: 345.79
CAS Registry Number: 59333-67-4
Laboratory code: None listed



2 page(s)
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Commercial &
TRADE
Secret

Dissolution specification and Test method | Pending | Refer to BioPharm. review

COMMENTS:

1. NDA 18-936 is referenced for the drug substance fluoxetine hydrochloride, USP. The fluoxetine hydrochloride,USP monograph became effective on 11/15/97 and NDA 18-936 has been updated to conform to the fluoxetine hydrochloride, USP monograph.
2. The following CMC sections of the submission are acceptable: **Drug Substance**; **Drug Product**: components/composition; specifications & methods for inactive components; manufacturer; methods of manufacturing and packaging; **Investigational Formulations**; **Environmental Assessment**; **Establishment Inspection**.
3. The following proposed specifications and tests are acceptable for both the 10mg and 20mg tablet. Physical Appearance; Identity; Assay; and Uniformity of Dosage Units. Once the Applicant responds to the method validation deficiency pertaining to Largest Individual Related Substance and Total Related Substances/ I will evaluate this proposed specification and test method. Refer to the BioPharm. review for the evaluation of the Dissolution test and specification.
4. On 1/14/99 I received from Eli Lilly a fax containing clarifying information needed to review the following packaging DMFs: DMF and I'm currently reviewing these DMFs. The corresponding packaging information will be reviewed once the following Type III DMFs have been found adequate: DMF
5. The following proposed stability specification and specification test method for both the 10mg and 20mg tablet are acceptable: Potency). Once the Applicant responds to the method validation deficiency pertaining to Largest Individual Related Substance and Total Related Substances/ , I will evaluate this proposed specification and test method. Refer to the BioPharm. review of the Dissolution test and specification.
6. As a follow-up to the inspection requests I submitted on 4/29/98, on 1/14/99 I checked the EES database for these 2 sites. Both sites are still in good standing: CFN 1819470 and CFN 2518332.

CONCLUSIONS: For the CMC section of the submission, it is Approvable. See draft deficiency letter.

The Applicant proposed a 24 month expiration period at controlled room temperature 20° to 25°C for the 10mg and 20mg Prozac® Tablets. Based on the primary stability information submitted, I can only reach a conclusion for the tablets packaged in the following bottles.

1. 10mg tablet, 30count bottle, closure: 24 month expiration period: Acceptable
2. 10mg tablet, 100count bottle, closure: 24 month expiration period: Acceptable.
3. 10mg tablet, 2000count bottle, screw closure: 24 month expiration period: Acceptable.
4. 20mg tablet, 30count bottle, closure: 24 month expiration period: Acceptable.
5. 20mg tablet, 100count bottle, screw closure: 24 month expiration period: Acceptable.
6. 20mg tablet, 2000count bottle, screw closure: 24 month expiration period: Acceptable.

Once the Applicant addresses the packaging/stability blister-pack deficiencies, I can comment on the proposed expiration period for the blister packaging. Also, additional information is needed from the Applicant regarding the 10mg tablet, 100count bottle with screw closure and the 20mg tablet, 100count bottle with closure

/S/ 1/19/99

Donald N. Klein, Ph.D.
Review Chemist, HFD-120

/S/ 1.22.99 for

Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-974 **CHEM REVIEW: #2** **REVIEW DATE:** 2/24/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3/19/98	3/20/98	3/25/98
N(BC) Amendment	6/5/98	6/8/98	6/19/98
N(BC) Amendment	7/7/98	7/8/98	7/8/98
N(BC) Amendment	7/30/98	7/31/98	8/6/98
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N(BC) Amendment	8/24/98	8/25/98	9/1/98
N(BC) Amendment	8/26/98	8/27/98	9/1/98
N(BC) Amendment	9/21/98	9/22/98	9/29/98
N(BC) Amendment	9/29/98	9/30/98	10/1/98
N(BC) Amendment	11/20/98	11/23/98	12/2/98
N(BC) Amendment	2/18/99	2/19/98	2/23/99

NAME AND ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:

Proprietary:	Prozac® Tablets
Non proprietary/USAN:	Fluoxetine hydrochloride
Code Name/Number:	None
Chem. Type/Ther. Class:	1S

PHARMACOLOGICAL CATEGORY/INDICATION:

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SPECIAL PRODUCTS:	__Yes xx No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

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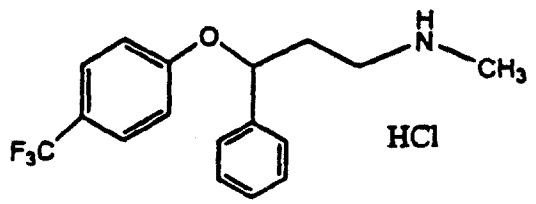
USAN Name: Fluoxetine Hydrochloride
Chemical Formula: $C_{17}H_{18}NOF_3$. HCl
Molecular Weight: 345.79
CAS Registry Number: 59333-67-4
Laboratory code: None listed



2 pages
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Apparatus: USP Dissolution Apparatus I at 100rpm.
Media: Deaerated 0.1N HCl of 1000mL at 37°C.
Specification: Q = at 15 minutes.

COMMENTS:

1. The CMC deficiencies were faxed to the Applicant on 1/25/99. I have reviewed the Applicant's responses to the deficiencies from chemistry review # 1 and all the responses are acceptable except the response to the Method Validation Question # 3.
2. The following CMC sections of the submission are acceptable: **Drug Substance; Drug Product:** components/composition; specifications & methods for inactive components; manufacturer; methods of manufacturing & packaging; specifications & methods; container/closure system; stability; **Investigational Formulations; Environmental Assessment; Method Validation; Establishment Inspection.**
3. It should be noted that in the 2/12/99 fax, Eli Lilly decided to withdraw the use of Closures'

CONCLUSIONS: For the CMC section of the submission, I recommend **Approval.** Refer to the draft deficiency letter.

The Applicant proposed a 24 month expiration period at controlled room temperature 20° to 25°C for the 10mg and 20mg Prozac® Tablets. This applies to both the bottles and the blister packaging.

/S/ 2/24/99

Donald N. Klein, Ph.D.
Review Chemist, HFD-120

/S/ 2/25/99

APPEARS THIS WAY

Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-974
HFD-120/Division File
HFD-810/CHoiberg
HFD-810/JSimmons
HFD-120/DKlein
HFD-120/RSeevers
HFD-120/AMosholder
HFD-120/PDavid
File: C:\hfd120\N20974\N20974RVW#2.doc

APPEARS THIS WAY
ON ORIGINAL