CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-936/S-033

Trade Name: Prozac

Generic Name: Fluoxetine hydrochloride

Sponsor: Lilly Research Laboratories

Approval Date: 01/09/1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-936/S-033

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Reviews / Information Included in this NDA Review.	
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Labeling	
Medical Review(s)	
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Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-936/S-033

APPROVAL LETTER

1191

JAN - 9 1995

NDA 18-936/S-033

Lilly Research Laboratories
Attention: M. W. Talbott, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

Please refer to your supplemental new drug application of August 17, 1993 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) Pulvules, 10 mg.

We also acknowledge your amendment of September 26, 1994 in response to the September 29, 1993 FDA letter regarding this supplement.

The supplement as amended provides for the manufacture, control, packaging, and labeling of Prozac (fluoxetine hydrochloride) Pulvules, 10 mg at your Carolina, Puerto Rico facility.

We have completed the review of this supplemental new drug application as amended and it is APPROVED.

It is our understanding that the stability studies in support of S-033 were conducted at your Indianapolis IN facilities [on product manufactured in Puerto Rico], and that it is your plan to have future stability studies for this strength product conducted in Puerto Rico once the facility is qualified. Please distinguish in your periodic reports where the stability studies were conducted.

We remind you of the reporting requirements of 21 CFR 314.80 and 314.81 for an approved application.

Sincerely yours,

Stanley W. Blum, Ph.D

Stanley W. Blum, Ph.D.
Supervisory Chemist
Division of Neuropharmacological Drug Products
Office of Drug Evaluation and Research
Center for Drug Evaluation and Research

cc: Original NDA 18-936
Div. File HFD-120/
/JRzeszotarski/ 09-JAN-95
/SWBlum/
/CSO/PDavid/
HFD-80
HFR-MW200 / DET-DO
HFR-SE400 / SJN-DO

ft/ET/01-06-95
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-936/S-033

NON-APPROVABLE LETTER

108-1

SEP 29 1993

NDA 18-936/S-033

Lilly Research Laboratories
Attn: M.W. Talbott, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

Please refer to your supplemental new drug application of 17-AUG-93 submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Pulvules No. 3104 Prozac 10 mg.

We have the following observations and requests regarding the Chemistry and Manufacturing Controls portions of your Notice:

1. We request that you elect one name for your drug product and use it routinely. At present we observed: "Pulvules No. 3104 Prozac 10 mg," (cover letter); "Pulvules Prozac 10 mg," (p 4); "PU3104 Prozac 10 mg capsules," (p 8); "Prozac Pulvules 3104, fluoxetine hydrochloride, 10 mg," (p 11); "PU3104 Pulvules Prozac 10 mg," etc.
2. Please correlate the lot numbers of PROZAC 10 mg manufactured at Carolina, PR and used in the accelerated and real time stability studies, with the lots of fluoxetine hydrochloride, their size and location of manufacturing. Kindly identify the location of the control facility(ies) that carried out the above stability studies.
3. Please provide a copy of the regulatory specifications and tests for the drug substance and the drug product.
4. Please provide the analytical results for the release tests for the lots of fluoxetine hydrochloride used in the stability studies of the drug product (see # 2) and the location of the control facilities that carried them out.
5. Please clearly identify what each of the three control facilities listed for the drug product (p 8) is assigned to do for the in-process testing and control.
6. We note your batch formula for [ ] PROZAC 10 mg, capsules (p 5) and the representative batch histories with formulae for [ ] PROZAC 10 mg, capsules (lots: 6LU00; 6LU01 and 6LU02)(pp 14 - 19). Further we note the manufacturing tickets (pp 79 - 103). Please state the desired batch size for the marketplace.
7. Kindly identify the equipment used or to be used in manufacturing of PROZAC 10 mg, capsules by type, model and capacity.
8. Please specify whether the capsules are to be imprinted by the supplier or at your facility and what acceptance test are to be performed. Kindly specify the composition of edible inks [ ] and [ ] and the tests to identify them.
9. Please specify which of the in-process and control testing of the finished dosage form may be performed at Eli Lilly and Company, Lilly Industrial Center, 1200 - 1555 Kentucky Ave,

Indianapolis, IN 46285 and which at Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

10. Please describe your in-process controls and tests.

11. Please describe your reprocessing operations. If none are planed, it should be clearly stated.

12. We note your description of PU3104 Prozac 10 mg, capsules (p 33): "Each capsule is imprinted with either the company logo, product name, strength and/or Identi-Code." Please explain when and why do you intend to use two distinctly different imprints.

13. Please clearly state whether your 30°C stability studies were done at controlled (45%RH) or monitored humidity conditions.

Should you have any questions regarding the above listed observations and requests please call Dr. Janusz Rzeszotarski, the reviewing chemist, at (301) 443-3870 or the CSO for this NDA Mr. Paul David.

Sincerly yours,

Stanley W. Blum PhD

Stanley Blum Ph.D.
Supervisory Chemist
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NOT APPROVED

cc: Original NDA 18-936/S-033
Division File /HFD-120
/HFD-120/TLaughren
/HFD-120/~~MMille~~ DAVID
/HFD-120/WJRzeszotarski
/HFD-120/SWBlum

filename: F:\RZESZOTARSKI\18936033/LET

HFD-130

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-936/S-033

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW OF SUPPLEMENT

1. ORGANIZATION:	HFD-120
2. NDA NUMBER:	18-936
4. SUPPLEMENT NUMBERS/DATES:	S-033
LETTERDATE	17-AUG-93
STAMPDATE	23-AUG-93
5. AMENDMENTS/REPORTS/DATES:	
LETTERDATE	
STAMPDATE	
6. REC'D BY CHM:	01-SEP-93

7. APPLICANT NAME AND ADDRESS:

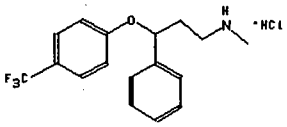
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

SEP 27 1993

8. NAME OF DRUG: **PROZAC®**

9. NONPROPRIETARY NAME: Fluoxetine hydrochloride

10. CHEMICAL NAME/STRUCTURE: (±)-N-Methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy]propylamine hydrochloride



11. DOSAGE FORM(S): *Capsules (Pulvules)*

12. POTENCY(IES): 10 mg eq to base

13. PHARM. CATEGORY: *ANTIDEPRESSANT*

14. HOW DISPENSED: XXX (Rx) ___ (OTC)

15. RECORDS AND REPORTSCURRENT: XXX (YES) ___ (NO)

16. RELATED IND/NDA/DMF(S): IND [redacted], NDA 20-101, NDA 20-187

17. SUPPLEMENT PROVIDES FOR: Manufacture, control, packaging, and labeling of Pulvules No 3104 Prozac 10 mg at Carolina, Puerto Rico.

18. COMMENTS: There are numerous deficiencies that would have to be clarified prior to approval.

19. CONCLUSIONS AND RECOMMENDATIONS: *Recommend the NDA 18-936.S-033* ***NOT APPROVED*** *until the deficiencies are resolved. See* ***REVIEW NOTES.***

20. REVIEWER NAME	*SIGNATURE*	*DATE COMPLETED*
W. Janusz Rzeszotarski, Ph.D.	W. J. Rzeszotarski	24-SEP-93

Copies:
[redacted]-936
HFD-120
HFD-120/PDavid
HFD-120/WJRzeszotarski/24-SEP-93
R/D Init by: SWB

filename: N018936.033

SWB 9/25/93

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review #1

JAN - 6 1995

CHEMISTS REVIEW

1. ORGANIZATION: HFD-120

2. NDA NUMBER: **18-936**

4. SUPPLEMENT NUMBERS/DATES: **S-033**

LETTERDATE 17-AUG-93
STAMPDATE 23-AUG-93

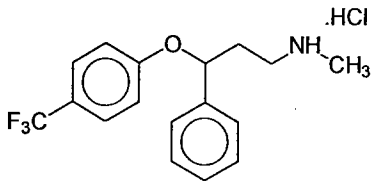
5. AMENDMENTS/REPORTS/DATES:

LETTERDATE 26-SEP-94
STAMPDATE 27-SEP-94

6. REC'D BY CHEMIST: 01-SEP-93, 29-SEP-94

7. APPLICANT NAME AND ADDRESS: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

8. NAME OF DRUG: Prozac® (Fluoxetine hydrochloride) Pulvules®



9. NONPROPRIETARY NAME: Fluoxetine hydrochloride

10. CHEMICAL NAME/STRUCTURE: (±)-N-Methyl-3-phenyl-3-[(*α*,*α*,*α*-trifluoro-p-tolyl)-oxy]propylamine hydrochloride

11. DOSAGE FORM(S): Capsules (Pulvules)

12. POTENCY(IES): 10 mg eq to base

13. PHARM. CATEGORY: Anitdepressant/Serotonin Uptake Inhibitor

14. HOW DISPENSED: XXX (Rx) (OTC)

15. RECORDS AND REPORTSCURRENT: XXX (YES) (NO)

16. RELATED IND/NDA/DMF(S): IND [ ]; NDA 20-101; NDA 20-187

17. SUPPLEMENT PROVIDES FOR: The amendment provides for a response to the deficiency letter issued on 29-SEP-93 by TSC Dr S.W. Blum.

18. COMMENTS: The response is satisfactory only in part. The most important information provided in response is the very low level of relative humidity (✓%) used in the stability studies that is not compatible with the humidity at the proposed manufacturing site - Puerto Rico. (See enclosed)

19. CONCLUSIONS AND RECOMMENDATIONS: Recommend NDA 18-936.S-033 as amended **NOT APPROVED**. Draft letter enclosed.

20. REVIEWER NAME | **SIGNATURE** | **DATE COMPLETED**

W. Janusz Rzeszotarski, Ph.D — 07-OCT-94

cc:
ORIG; NDA 18-936
HFD-120
HFD-120/PDavid
HFD-120/WJRzeszotarski/07-OCT-94
INIT: SWB/

filename: N018936.A33

SWB 1/6/95
see memo

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of trade secret and/or

confidential commercial

information from

Chemistry Review #2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

Blum

J

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)	DATE	PHONE NO.	EER ID #
Original XX Follow-Up ☐ FUR	31-OCT-94	594-5537	4152

REQUESTOR'S NAME	DIVISION	MAIL CODE
STANLEY W. BLUM, Ph.D.	NEUROPHARM	HFD- 120

APPLICATION AND SUPPLEMENT NUMBER: NDA 18-936 S-033

BRAND NAME	ESTABLISHED NAME
PROZAC PULVULES	FLUOXETINE HYDROCHLORIDE

DOSAGE AND STRENGTH	STERILE
10 mg capsule	☐ YES ☒ NO

PROFILE CLASS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)
CHG	

APPLICANT'S NAME: ELI LILLY

ADDRESS: INDIANAPOLIS, INDIANA 307 E. McCarty St 46285

COMMENTS

PLEASE SEE EER # 4022.

*** The Carolina P.R. site is already used and AP for making 20 mg capsules. [ ]

S-033 also includes manufacture of n.d.s. @ Tippecanoe Indiana and Mayagues, P.r. -- contract packaging by [ ]

alternate control facility/ies at Indiana site

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
1. ELI LILLY INDUSTRIS, INC. 12.6 Km 65th INFANTRY ROAD CAROLINA, PUERTO RICO 00985	Manufacture, control, pkging, labeling	CHG	ELC 19905	XC 12/22/94
2.				
3.				
4.				
5.				

FOR HFD-324 USE ONLY	CSO	DATE RECEIVED
	Annette Rogers	11/1/94
	CGMP COMPLIANCE STATUS: Acceptable	DATE 12/30/94

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-936/S-033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 18-936
S-033

Lilly Research Laboratories
ATTN: M.W. Talbott, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr Talbott:

Please refer to your supplemental new drug application of 17-AUG-93 submitted pursuant to section 505 (b) of the Federal Food, drug, and Cosmetic Act for Prozac® (fluoxetine hydrochloride) Pulvules® 10 mg.

Reference is also made to your letter dated 26-SEP-94 amending this supplemental application.

We have reviewed the above application as amended and it is NOT APPROVED.

We have the following observations and requests regarding the Chemistry and Manufacturing Controls portion of your Notice:

1. In reference to your regulatory specifications and tests we request that you modify your limits for heavy metals to [ ].

2. We further request that you establish for fluoxetine hydrochloride [ ] drug substance a particle size range within which / % of the particle will be included.

3. Kindly clarify your response # 4. The table provided does not indicate whether the [ ] [ ].

4. In reference to your response # 8 we request that you describe in detail <u>your</u> acceptance tests to be performed <u>by you</u> on the [ ] capsules. We insist that you carry out <u>your own</u> ink identification tests as part of the acceptance procedure.

5. We find the relative humidity of your proposed stability studies (your response # 13) too low to reflect the persisting conditions at the proposed site of manufacturing in Puerto Rico. We request that the 30°C stability studies be carried out at no less than 45% relative humidity.

Should you have any questions regarding the above listed observations and requests please call Dr Janusz Rzeszotarski, the reviewing chemist at (301) 594-5550 or the CSO for this NDA Mr Paul David at (301) 594-5530.

Sincerely yours,

Paul Leber, M.D.
Director, etc.

119-1

Lilly ORIGINAL NDA SUPPL AMEND

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

September 26, 1994

(AC)
NDA NO. 18-936 REF. NO. SCM033
NDA SUPPL FOR Manufacturing Change

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-936, Prozac® (fluoxetine hydrochloride) - Pulvule®

This supplement amendment is in response to a letter dated September 29, 1993 from Dr. Stanley Blum, Supervisory Chemist, Division of Neuropharmacological Drug Products (FDA). This letter stated deficiencies in our supplement to NDA 18-936 Prozac which was submitted to the FDA August 17, 1993. The supplement provided for the manufacture, control, packaging, and labeling of Prozac pulvules 10 mg at our Carolina, Puerto Rico facility.

This supplement amendment provides responses to the questions.

Please call Dr. Al Webber at (317) 276-4255, Dr. Richard Raths at (317) 276-4248) or me at (317) 276-2574 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Director
Worldwide Regulatory Affairs

Enc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date August 24, 1993

NDA No. 18-936

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Attention: M.W.Talbott, Ph.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: PROZAC - Pulvules

NDA Number: 18-936

Supplement Number: S-033

Date of Supplement: August 17, 1993

Date of Receipt: August 23, 1993

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 10B-20
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

For John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research

cso: David

ORIGINAL

NDA SUPPLEMENT

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

NDA NO. 18-936 REF. NO. SCM033

NDA SUPPL FOR Manufacturing change

August 17, 1993

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room 10B-20
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-936 - Prozac® (fluoxetine hydrochloride)

We are submitting herewith a supplement to the referenced NDA. This supplement provides for the manufacture, control, packaging, and labeling of Pulvules No. 3104 Prozac 10 mg at Carolina, Puerto Rico.

Please call me at (317) 276-2574 or Dr. Al Webber at (317) 276-4255 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

M. W. Talbott, Ph.D.
Director
Worldwide Regulatory Affairs

Enc.