

Note to Rev. Div. M.O.

This routine inspection was conducted in support of pending NDA 21-235 and focused on the conduct of protocol B1Y-MC-HCIZ.

Forty-four (44) subjects were screened at this site; thirty-seven (37) were enrolled (i.e., entered Period II); and eighteen (18) subjects were randomized (i.e., entered Period III).

Records from nine (9) subjects were reviewed. No deviations from federal regulations were noted.

Data acceptable

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ON ORIGINAL



8.1

NDA 21-235

AUG 25 2000

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your pending new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac \_\_\_\_\_ (fluoxetine hydrochloride) 90 mg Capsules.

Our review of your proposed tradename of Prozac \_\_\_\_\_ is complete, and we have found it unacceptable for the following reasons:

1. The \_\_\_\_\_ portion of the name is believed to be fanciful and misleading in that it implies a unique effectiveness or composition of the product that does not exist (see 21 CFR 201.10(c)(3)). \_\_\_\_\_ implies that the product has unique extended-release properties and, therefore, a unique effectiveness as compared with fluoxetine HC1 (Prozac) immediate-release capsules or other fluoxetine HC1 dosage forms. In fact, the product's effectiveness with a weekly dosing schedule and subsequent \_\_\_\_\_ of action relate primarily to the unusually long half-life of the drug substance itself, fluoxetine HC1, and its metabolites. The active drug substance is merely delayed by 1 to 2 hours after it reaches lower portions of the gastrointestinal tract. This is due to formulation of the product as enteric-coated granules inside a gelatin capsule. Weekly dosing and the extended duration of action are principally due to the pharmacokinetic properties of fluoxetine HC1 itself, not the \_\_\_\_\_ dosage form. Thus, the use of the name \_\_\_\_\_ exaggerates the benefits of the dosage form over the existing, immediate-release and creates an impression of greater value of the inert ingredients (e.g., enteric-coating) than their true functional role in the formulation (see 21 CFR 201.10(c)(4)).
2. We have also concluded that there may be confusion regarding the word ending \_\_\_\_\_. The modifier \_\_\_\_\_ is misleading as to its true function. A number of products in the U.S. contain the word ending \_\_\_\_\_, or \_\_\_\_\_, all of which consistently denote a unit-of-use package with more than one dosage unit. We suggest that Lilly follow the usual practice of adding a modifier to the name Prozac that would more accurately reflect the nature of this product (e.g., a delayed-release formulation of the existing drug substance).
3. We request that the established name of this product be revised to "Fluoxetine Delayed-Release Capsules" (throughout the labeling provided, Lilly refers to the dosage form as \_\_\_\_\_). This is a dosage form modifier that is not officially recognized by the United States Pharmacopeia in their official compendia and is also not accurate in describing the product. Enteric-coated capsules are specifically discussed in the USP/NF under Delayed-Release Capsules.

Therefore, the established name of this product needs to be revised to comply with the USP/NF standard nomenclature.

Please resubmit a proposed tradename and established name for the Agency to review.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

[ ISI ]

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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ON ORIGINAL

NDA 21-235

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cc:

Archival NDA 21-235

HFD-120/Div. Files

HFD-120/P.David

HFD-120/RKatz/T.Laughren

HFD-120/K.Smith/A.Mosholder

HFD-120/G.Fitzgerald/B.Rosloff

HFD-120/RSeevers/GGill-Sangha

HFD-860/RBaweja

HFD-710/KJin

151 8-24-00

151 8/23/00

DISTRICT OFFICE

8/23/00pd

filename: PROZAC' \_\_\_\_\_ N21235' \_\_\_\_\_ UNACCEPTABLE LETTER TO LILLY.DOC

**DISCIPLINE REVIEW LETTER (DR)**

APPEARS THIS WAY  
ON ORIGINAL

David

# Electronic Mail Message

**Date:** 8/22/00 10:19:44 AM  
**From:** Paul David (DNPDP/ODEI) ( DAVID )  
**To:** Tarwater\_O\_Reed ( Tarwater\_O\_Reed@lilly.com )  
**Cc:** Paul David (DNPDP/ODEI) ( DAVID )  
**Subject:** Prozac ——— - Clinical Questions

Reed,  
 The reviewing medical officer has the following questions in regard to the Prozac ——— application, NDA 21-235:

1. Please clarify the definition of baseline in regards to vital sign measurement. The report measures change from baseline to endpoint. Endpoint (for Study Period III) is Visit 18 at the end of Study Period III. Is baseline the screening vital sign measurement (visit 1) or is it visit 8 at the beginning of Study Period III?

2. Please provide the Agency with a list of the primary investigators, their addresses, center number, and number of patients they contributed to in study BLY-MC-HCIZ.

If you have any questions regarding this request, please contact me.

Paul David,  
 Regulatory Project Manager

APPEARS THIS WAY  
 ON ORIGINAL

AUG 22 2000

[ 151 8-22-00 ]

**BEST POSSIBLE COPY**

NDA 21-235  
 HFD-120 / D. FILE  
 HFD-120 / R. L. / Thuyhien  
 HFD-120 / Adosh. / K. Smith  
 HFD-120 / P. David



DEPARTMENT OF HEALTH & HUMAN SERVICES

*P. David*  
Public Health Service  
Food and Drug Administration  
Rockville MD 20857

NDA 21-235

AUG 16 2000

Eli Lilly and Company  
Attention: Gretchen Bowker  
CM&C Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Ms. Bowker:

Please refer to your new drug application (NDA) submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac — 90 Delayed Release Capsules.

Reference is also made to a conference call meeting between representatives of your firm and FDA on July 18, 2000. The purpose of the meeting was to discuss the Agency deficiency letter dated July 3, 2000.

We acknowledge receipt of your submission dated August 2, 2000, providing for your version of the July 18, 2000 meeting minutes.

We have completed our review of your meeting minutes, and we believe that they accurately reflect the record of the meeting.

Therefore, we consider these minutes as the official minutes of the meeting.

If you have any questions, contact Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

[ *LSI* ] *8/16/00*

Robert H. Seevers, Ph.D.  
Chemistry Team Leader, Psychiatric Drugs for the  
Division of Neuropharmacological Drug Products, (HFD-120)  
DNDC I, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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NDA 21-235

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Original NDA 21-235

HFD-120/Div. File

HFD-120/R.Katz/T.Laughren

HFD-120/R.Seevers/G.Gill-Sangha 151, 3/10/00

HFD-120/P.David *SA 8-18-00*

filename: PROZAC\ ——— NDA\7-18-00 MEETING MINUTES LETTER TO LILLY.DOC

GENERAL CORRESPONDENCE (MINUTES SENT)

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p. David

AUG 3 - 2000



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-235

**DISCIPLINE REVIEW LETTER**

AUG 3 - 2000

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, US Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your 19 July 2000 submission for new drug application (NDA 21-235) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac® \_\_\_\_\_ 90 mg delayed release capsule.

Our review of the Chemistry section of your submissions is complete, and we have identified the following deficiencies:

1. Please include the word "discrete" to signify that the enteric coated pellets are not stuck together and individually visible from the clear body of the capsule in the physical appearance statement of drug product specifications.
2. \_\_\_\_\_ and other reference compounds for N21235 must be provided to FDA laboratories. In addition, provide detailed chromatograms of all reference compounds establishing the % purity. \_\_\_\_\_ in its current state of purity must not be used in any quantitative method.
3. Please commit to always running methods \_\_\_\_\_ and \_\_\_\_\_ for \_\_\_\_\_ minutes as specified to ensure detection of \_\_\_\_\_.
4. Please add \_\_\_\_\_ to the list of samples for FDA labs.
5. All the changes and additional information reported for methods validation section as per amendment 19-July-2000 must be included in the updated FDA laboratory copy for methods validation.
6. The corrected relative retention times in amendment 19-Jul-2000 for Table 1, page 220, Vol. 1.2 are still incorrect. The corrected times for related compounds based on

retention time of fluoxetine are \_\_\_\_\_ Please provide rationale for the relative retention numbers reported for corrected table in amendment 19-Jul-2000.

7. The accuracy of the method is proposed due to high extinction coefficient values of fluoxetine compared to other related substances. The response to Q5 xiv) in amendment 19-Jul-2000 did not provide data to support the statement. Please provide extinction coefficient values for fluoxetine and other related substances.
8. The how supplied section of the package insert must include accurate physical description of Prozac® \_\_\_\_\_. Please change the sentence in how supplied section of Prozac® \_\_\_\_\_ to "The 90 mg capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with "Lilly" on the cap, and "3004" and "90 mg" on the body".

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

[ RS ] 8/3/00

Robert H. Seevers, Ph.D.  
Chemistry Team Leader, Psychiatric Drugs for the  
Division of Neuropharmacological Drug Products, (HFD-120)  
DNDC I, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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NDA 21-235

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Archival NDA 21-235

HFD-120/Div. Files

HFD-120/PDavid

HFD-120/RSeevers

HFD-120/GGill-Sangha

HFD-810/DNDC Division Director - only for CMC related issues

DISTRICT OFFICE

Drafted by: ggs/Aug 3, 2000

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DISCIPLINE REVIEW LETTER (DR)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville MD 20857

P. David

NDA 21-235

**DISCIPLINE REVIEW LETTER**

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, US Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

JUL 3 2000

Dear Dr. Brophy:

Please refer to your 13 February, 2000 (presubmission) new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac® \_\_\_\_\_ 90 mg delayed release capsule.

We also refer to your submissions dated 13 March, 2000 (original), amendments dated 16 March, 24 March, 28 March, 13 April, 1 May, 18 May and 22 May 2000.

Our review of the Chemistry section of your submissions is complete, and we have identified the following deficiencies:

- 1. Please commit to reporting the changes in conditions and equipment related to reprocessing appropriately in a supplement or annual report as per the Guidance for Changes to an Approved NDA or ANDA, November 1999.**
- 2. Prozac® \_\_\_\_\_ capsules visibly show discrete pellets through the clear body of the capsule. Please add to the physical appearance of drug product specifications that the enteric coated pellets are discretely visible through the clear body of the capsule.**
- 3. \_\_\_\_\_ is an impure compound as reported in the NDA, and therefore must not be used as reference standard. Please use new pure lots of this reference standard and provide the pure sample for methods validation to the FDA laboratories.**
- 4. i) \_\_\_\_\_ is a possible impurity similar to the \_\_\_\_\_ due to use of \_\_\_\_\_ as enteric coating material. Can your isocratic HPLC method \_\_\_\_\_, detect \_\_\_\_\_? As per the article in \_\_\_\_\_**

Chromatographia, 1997, 46, (9-10), 511-523 by Lilly Research Laboratories,

\_\_\_\_\_ can only be differentiated from \_\_\_\_\_ using \_\_\_\_\_ HPLC method. Please provide data to support the evidence for lack of \_\_\_\_\_ in the drug product specifications. In addition please provide the chromatograms reflecting retention times of a known sample of \_\_\_\_\_ and drug product using the same HPLC method. The chromatograms must also include a sample spiked with control \_\_\_\_\_ to differentiate from the drug product and other impurities. If \_\_\_\_\_ is detected in the drug product, the results must be incorporated in the drug product specifications, analytical methods and methods validation sections.

ii) Please include \_\_\_\_\_ as part of specifications for the incoming lots of \_\_\_\_\_

5. The following clarifications pertain to the analytical methods and methods validation section:

- i) Please define the placebo lot used in method \_\_\_\_\_ (pages 30-37, 150-157, Vol. 1.2) and clarify the peaks observed for the placebo lot.
- ii) Provide correlation between the active lot numbers to the batch/lot numbers of the drug product submitted in the NDA for method \_\_\_\_\_
- iii) Please provide data (HPLC chromatograms) correlating fluoxetine from pellets to the fluoxetine HCl reference standard for method \_\_\_\_\_
- iv) The data for the analytical methods and methods validation section shows that the retention time of impurities shifts relative to the fluoxetine peak using HPLC methods \_\_\_\_\_ and \_\_\_\_\_. Provide chromatograms identifying fluoxetine from other related substances for method \_\_\_\_\_ to establish absence of impurities co-eluting with fluoxetine peak.
- v) The data from method \_\_\_\_\_ does not report detection of \_\_\_\_\_ and shows that \_\_\_\_\_ elutes close to fluoxetine. Therefore, provide data clarification to support accurate assay calculations of fluoxetine using method \_\_\_\_\_
- vi) Please provide consistent information for reporting the compounds either by codes or by chemical names in methods validation and analytical methods section. Provide a table summarizing the codes and names of corresponding compounds for methods validation to FDA laboratories.
- vii) Summarize the method parameters for each specification method in a comprehensive format at the beginning of the analytical or methods validation section. For example, for method \_\_\_\_\_ list the final parameters used such as run time, column type, sample solvent, mobile phase, detection wavelength, wash and equilibrium time and conditions.
- viii) Provide rationale for using \_\_\_\_\_ mobile phase in method \_\_\_\_\_ compared to \_\_\_\_\_ in method \_\_\_\_\_
- ix) \_\_\_\_\_ co-elutes with \_\_\_\_\_ using method \_\_\_\_\_. The validation data states that \_\_\_\_\_ is a process impurity and not a related substance. However, the method used for related substances must resolve all

the impurities in the drug product. Please provide rationale for using method \_\_\_\_\_ for determination of related substances even though the method is unable to resolve all the impurities.

- x) Provide corrected values for relative retention in Table 1, page 220, Vol. 1.2.
- xi) \_\_\_\_\_ and \_\_\_\_\_ are listed as the primary and secondary methods respectively for determining the related substances. Please clarify the method used for determination of related substances in drug product specifications and stability protocols.
- xii) Please provide information on sample preparation for fluoxetine from pellets for method \_\_\_\_\_ similar to the reference standard in 0.1 N HCl and pH 6.8 buffer as reported on page 239, Vol. 1.2.
- xiii) Define the contents of placebo material resulting in high interference as reported on page 258, Vol. 1.2 for method \_\_\_\_\_
- xiv) The \_\_\_\_\_ method of detection for dissolution assay relies on specificity based on high extinction coefficient of fluoxetine. Provide extinction coefficient of related substances and calculated effect of other related substances on the dissolution values obtained by \_\_\_\_\_ method.

6. Amendment dated 22 May 2000 provided a table listing the container closure components from specific vendors on stability studies. The table also highlighted certain alternate vendors and therefore, no stability studies were reported using components from alternate vendors. Please note that based on acceptable stability data only the following container closures are approved for packaging Prozac®

\_\_\_\_\_:

Bottles	Blisters
<ul style="list-style-type: none"><li>•</li><li>•</li><li>•</li><li>•</li></ul>	

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified.

In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify

other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

[ ISI ] 7/3/00

Robert H. Séevers, Ph.D.

Chemistry Team Leader, Psychiatric Drugs for the  
Division of Neuropharmacological Drug Products, (HFD-120)  
DNDC I, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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ON ORIGINAL

NDA 21-235

Page 5

cc:

Archival NDA 21-235

HFD-120/Div. Files

HFD-120/PDavid

HFD-120/RSeEVERS

HFD-120/GGill-Sangha

HFD-810/DNDC Division Director - only for CMC related issues

DISTRICT OFFICE

Drafted by: ggs/June 29, 2000

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DISCIPLINE REVIEW LETTER (DR)

APPEARS THIS WAY  
ON ORIGINAL

P. David

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** April 26, 2000  
**Time:** 10:00 AM  
**Location:** Conference Room E; WOC2  
**Application:** NDA 21-235; Prozac (fluoxetine HCl) 90 mg Capsules; Lilly  
**Type of Meeting:** Internal 45 Day File/Refuse to File Meeting  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Paul David, R.Ph.

### FDA Attendees:

HFD-120: Drs. Russell Katz, Thomas Laughren, Kathy Smith, Andrew Mosholder, Glenna Fitzgerald, Barry Rosloff, Robert Seevers, Gupreet Gill-Sangha, Mr. Paul David  
HFD-710: Drs. Kun Jin, Ohidul Siddiqui  
HFD-860: Drs. Ray Baweja, Vanitha Sekar  
HFD-340: Dr. Constance Lewin

### PURPOSE:

- The purpose of the meeting was to make a threshold determination whether there was sufficient information contained in the NDA for a substantive review of the application. The NDA application was dated March 13, and received on March 14, 2000. The primary UF goal date is January 14, 2001, and the secondary goal date is March 14, 2001.

### DISCUSSION:

#### CMC

- The drug product contains a new excipient, \_\_\_\_\_, which would be the first approval of this new excipient in the US.
- Lilly has proposed a \_\_\_\_\_ months expiration date based upon the stability data submitted.
- The 90 mg delayed release capsule is a green capsule with a clear body. There may be some product identification confusion with the 20 mg immediate release capsule which is a green capsule with an off white body. We will request representative samples for all of the marketed Prozac products.
- Lilly changed the dissolution methodology at \_\_\_\_\_ months into the stability studies, but this will be a matter of review.
- The application is fileable, from a CMC perspective, and the completion date will be 8-15-00.

#### Biopharmaceutics

- Lilly has submitted studies comparing the bioavailability of the 90 mg delayed release and the 20 mg immediate release capsules (the effect of food has also been evaluated). A multiple dose pK study using the 90 mg delayed release capsule has also been submitted.
- The application is fileable, from a biopharmaceutics perspective, and the completion date will be 9-1-00.

#### Pharm/Tox

- The majority of the preclinical data was referenced in the immediate release fluoxetine application, NDA 18-936. However, Lilly did provide preclinical data on the \_\_\_\_\_ excipient.
- The application is fileable, from a pharm/tox perspective, and the completion date will be 9-1-00.

**Statistical/Clinical**

- The application is fileable, from the statistical and clinical perspectives, and the completion date will be 9-1-00.

**CONCLUSION/ACTION ITEMS**

- The application is fileable, and all reviews will be completed by 9-1-00.
- The Division will request representative samples of fluoxetine products from Lilly.
- DSI will inspect the pivotal trial, HCIZ.

Minutes Preparer:

          /S/          

Paul A. David, R.Ph.  
Regulatory Project Manager, DNDP

Chair Concurrence:

          /S/            
(or designated signatory)

5-15-00

cc:

Archival NDA 21-235  
HFD-120/Div. Files  
HFD-120/P.David  
HFD-120/R.Katz/T.Laughren/A.Mosholder/K.Smith  
HFD-120/G.Fitzgerald/B.Rosloff  
HFD-120/R.Seevers/G.Gill-Sangha  
HFD-860/R.Baweja/V.Sekar  
HFD-710/K.Jin/O.Siddiqui  
rd: 5/2/00pd  
rev:5/2/00vs  
ft:5/15/00pd  
Doc #PROZAC' \_\_\_\_\_ NDA 21-235\4-26-00 45 DAY RTF MINUTES.DOC  
MEETING MINUTES

Chen 2/16

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** April 26, 2000

**DUE DATE:** September 1, 2000

**OPDRA CONSULT #:** 00-0135

**TO:** Russell Katz, M.D.  
Director, Division of Neuropharmacological Drug Products  
HFD-120

**COMPLETED** AUG 17 2000  
P. 25

**THROUGH:** Lana Chen, Project Manager  
HFD-120

**PRODUCT NAME:** Prozac  
(fluoxetine hydrochloride delayed-release capsules, 90 mg)

**MANUFACTURER:** Eli Lilly and Company  
Indianapolis, IN 46285

**NDA #:** 21-235

**SAFETY EVALUATOR:** Carol Pamer, R.Ph.

**SUMMARY:** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA conducted a review of the proposed proprietary name "Prozac" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:** OPDRA does not recommend use of the proprietary name "Prozac". The established name of this product also needs to be changed to comply with USP/NF standards.

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**  
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**  
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS**  
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

[ 151 ]  
Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
F: (301) 480-8173

[ 151 ] 8-11-2000  
Peter Honig, M.D.  
Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Office of Postmarketing Drug Risk Assessment (OPDRA)**

**HFD-400; Parklawn Building Room 15B-03**

**FDA Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** July 20, 2000

**NDA NUMBER:** 21-235

**NAME OF DRUG:** Prozac \_\_\_\_\_  
(fluoxetine hydrochloride delayed-release capsules, 90 mg)

**NDA HOLDER:** Eli Lilly and Company  
Indianapolis, IN 46285

**I. INTRODUCTION**

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the proprietary name Prozac \_\_\_\_\_. The Division (HFD-120) stated in the consult request that they do not have any concerns with this proposed name.

\_\_\_\_\_ is a delayed-release capsule intended for once-weekly dosing. The dosage form consists of enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg of fluoxetine enclosed in a gelatin capsule<sup>1</sup>. These pellets resist dissolution until reaching the segment of the gastrointestinal tract where the pH exceeds 5.5. The coating delays the onset of absorption of fluoxetine 1 to 2 hours, relative to the immediate release Prozac<sup>TM</sup> formulations. Like Prozac, \_\_\_\_\_ is indicated for the treatment of depression. \_\_\_\_\_ capsules will be supplied in bottles of 4, 12, 24, and 1000 capsules and blister packages of 4 and 12 capsules.

Administration of \_\_\_\_\_ once weekly provides plasma concentrations of fluoxetine and norfluoxetine that have a greater difference between peak and trough levels, as compared with once-daily dosing. Peak concentrations are in range of the average concentrations achieved with once daily dosing for 20-mg capsules. Trough concentrations are lower than those achieved with 20-mg once-daily dosing.

The sponsor of this NDA, Eli Lilly, also holds the NDA for Prozac (18-936, fluoxetine HCl) immediate release capsules. The patent for these products will expire on February 2, 2001.

## II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts<sup>ii,iii,iv</sup> as well as several FDA databases<sup>v</sup> for existing drug names which sound alike or look alike to *Prozac* \_\_\_\_\_ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's (USPTO) Text and Image Database was also conducted<sup>vi</sup>. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted a survey to elicit comments from FDA health professionals regarding their impression of the proposed proprietary name "*Proza* \_\_\_\_\_".

### A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name *Prozac* \_\_\_\_\_. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

*Several proprietary names were identified which contained the phrase \_\_\_\_\_, all of which refer to extended-release dosage forms. Prozac \_\_\_\_\_ is a delayed-release product, consisting of enteric-coated granules contained in a gelatin capsule. A number of products are also currently marketed in the U.S. with the suffix ' \_\_\_\_\_ or \_\_\_\_\_', all of which refer to multiple day-supply packaging configurations. The dosage forms and usual dosing of these similar products appear in Table 1 (see page 4). Confusion of Prozac \_\_\_\_\_ with products with the initial word phrase \_\_\_\_\_ seems unlikely, due to the unique dosing schedule of this product.*

*There were objections to the name of this product related to DDMAC concerns. The \_\_\_\_\_ portion of the name is believed to be fanciful and misleading in that it implies a unique effectiveness or composition of the product that does not exist (see 21 CFR 201.10(c)(3)). \_\_\_\_\_ implies that the product has unique extended-release properties and, therefore, a unique effectiveness as compared with fluoxetine HCl (Prozac) immediate-release capsules or other fluoxetine HCl dosage forms. In fact, the product's effectiveness with a weekly dosing schedule and subsequent \_\_\_\_\_ of action relate primarily to the unusually long half-life of the drug substance itself, fluoxetine HCl, and its metabolites.*

*The Expert Panel also concluded that the name "*Prozac* \_\_\_\_\_" was confusing in that \_\_\_\_\_ implies more than one capsule in a packaging configuration and multiple days of medication. The nomenclature structure is inconsistent with the existing products and seems likely to result in significant confusion.*

TABLE 1

Product Name	Dosage Form(s), Generic name	Usual adult dose	Other
Prozac	Oral: 90 mg delayed-release capsule (fluoxetine)	One capsule weekly	Enteric-coated granules, gelatin cap
	Oral: 4 mg chlorpheniramine, 60 mg pseudoephedrine <i>extended-release cap</i>	Child: 6-12: 1 cap twice daily.	Dura Pharmaceuticals
	Oral: 75 mg phenylpropanolamine, guaifenesin 300mg <i>extended-release tab</i>	Child 6-12: 1/2 tablet twice daily. Adult: One tablet twice daily.	
	Oral: 8mg chlorpheniramine, 20mg phenylephrine, 2.5mg methscopolamine <i>extended-release tab</i>	Child 6-12: 1/2 tablet twice daily. Adult: One tablet twice daily.	
	Oral: 324 mg <i>extended-release tab</i> (quinidine gluconate)	Adult: 1 to 2 tablets every 8 hours.	No addn'l "Quinaglute" product
Z-Pak	Oral: Packaging for azithromycin 250 mg, 6 tablets/5 day-supply	Adult: 2 tabs first day, then one every day until gone.	
Prevpac	Oral: Packaging for amoxicillin, clarithromycin, lansoprazole. 14 cards w/one day supply of 3 different drugs.	Adult: lansoprazole 30mg, amoxicillin 1 gram, clarithromycin 500mg twice daily for 14 days.	
Monistat Dual Pak	Vaginal: Packaging for miconazole 3-200mg suppositories and cream 2%	Adults: Use daily for 3 days.	
M-Zole 3 Combination Pack	Vaginal: Packaging for miconazole 3-200mg suppositories and cream 2%	Adults: Use daily for 3 days.	
Monistat 7 Combination Pack	Vaginal: Packaging for miconazole 7-100mg suppositories and cream 2%	Adults: Use daily for 7 days.	
M-Zole 7 Dual Pack	Vaginal: Packaging for miconazole 7-100mg suppositories and cream 2%	Adults: Use daily for 7 days.	
Flonin UroPak	Oral: Packaging for ofloxacin 200mg tabs, 6 tabs/3 days	Adults: One twice daily for 3 days.	
Medrol Dosepak	Oral: Packaging for total of 21 methylprednisolone 4 mg tabs	Adults: Take in specified tapering doses, for 6 days.	

**B. STUDY CONDUCTED BY OPDRA**

**1. Methodology**

A study was conducted within FDA employing a total of 93 health care professionals (nurses, pharmacists, and physicians) to determine the degree of confusion of Prozac with other U.S. drug products.

The study participants were provided, via email, basic product information that consisted of the following: "Prozac is a 90 mg capsule that will be dosed once weekly". Because Prozac is a tradename already in the marketplace, participants were asked to comment on the proposed name directly, rather than interpret handwritten and verbal prescriptions.

**2. Results**

We received responses from 45 of the 93 study participants. Ten (10) of these participants voiced no concerns about the name Prozac. *Eleven (11) respondents noted multiple sound-alike, look-alike names, which included the following:*

*PrevPac, and Procardia 90 mg.*

*Additionally, five (5) respondents stated that the name would likely be abbreviated to "Prozac 90 mg" in clinical practice settings and thus be confused with Prozac/fluoxetine immediate release*

capsules. Three (3) comments were received in which the respondents believed the name did not accurately or specifically convey the function of the capsule's extended/weekly dosing. *Fifteen (15) participants believed that the name "Prozac 90" referred to a packaging configuration of multiple doses or to a durable form of blister packaging.* One (1) participant noted the potential for confusion of "Prozac 90" with the standardized packaging terms "Blister Pack", "Dialpack", "Cello Pack" and "DosePak". *Another comment was received that the "90" portion of the name implied a longer than average duration of action.*

### C. SAFETY EVALUATOR RISK ASSESSMENT

*In the Expert Panel Discussion, a number of currently marketed U.S. product names were identified that contained the initial word phrase "Prozac" and these names consistently referred to extended-release products. Because of the unique dosage schedule of Prozac 90, it seems unlikely that the product would be confused with other sound-alike, look-alike products that begin with the word phrase "Prozac". However, the possibility of prescribers abbreviating the product name to "Prozac 90 mg cap" is likely, although the rates of release of the active drug substance from the two products is similar. Prozac 90 capsules are enteric-coated granules with a delayed release of 1 to 2 hours versus the immediate release formulation.*

*The name "Prozac 90" was believed to be misleading in that it implies that the capsule has extended-release properties. In fact, release of the active drug substance is merely delayed by 1 to 2 hours after it reaches lower portions of the gastrointestinal tract. This is due to formulation of the product as enteric-coated granules inside a gelatin capsule. Weekly dosing and the extended duration of action are principally due to the pharmacokinetic properties of fluoxetine HCl itself, not the "90" dosage form. Thus, the use of the name "Prozac 90" exaggerates the benefits of the dosage form over the existing, immediate-release products (see 21 CFR 201.10(c)(3)) and creates an impression of greater value of the inert ingredients (e.g., enteric-coating) than their true functional role in the formulation (see 21 CFR 201.10(c)(4)).*

*Confusion regarding the word ending "90" also seems likely. The modifier "90" is misleading as to its true function. A number of products in the U.S. contain the word ending "90", or "90s", all of which consistently denote a unit-of-use package with more than one dosage unit. We suggest that the sponsor follow the usual practice of adding a modifier to the name Prozac that would more accurately reflect the nature of this product (e.g., a delayed-release formulation of the existing drug substance).*

We conducted a survey among FDA health professionals and these impressions were confirmed by our study participants.

*For these reasons, we do not recommend use of the proprietary name "Prozac 90"*

### **III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES**

In our review of the cartons and package insert for Prozac 90, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified areas of possible improvement, in the interest of minimizing potential user error.

A. DRUG NOMENCLATURE ISSUES

The established name of this product should be revised to "Fluoxetine Delayed-Release Capsules"<sup>1</sup>. Throughout the labeling provided, the manufacturer refers to the dosage form as "\_\_\_\_\_". This is a dosage form modifier that is not officially recognized by the United States Pharmacopeia in their official compendia and is also not accurate in describing the product. Enteric-coated capsules are specifically discussed in the USP/NF under Delayed-Release Capsules<sup>vii</sup>.

**IV. RECOMMENDATIONS**

- A. OPDRA does not recommend use of the proprietary name "Prozac \_\_\_\_\_"
- B. The established name of this product needs to be revised to comply with the USP/NF standard nomenclature.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

[ 151 ]

\_\_\_\_\_  
Carol Pamer, R.Ph.  
Safety Evaluator  
Office of Postmarketing Drug Risk Assessment (OPDRA)

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Concur:

[ 151 ] 8/11/2000

\_\_\_\_\_  
Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Postmarketing Drug Risk Assessment (OPDRA)

<sup>1</sup> Consult per Daniel Boring, Chemist, FDA Labeling and Nomenclature Committee. August 4, 2000.

cc:

NDA 21-235

HFD-120: Division Files/Lana Chen, Project Manager

HFD-120: Russell Katz, Division Director

HFD-400: Jerry Phillips, Associate Director, OPDRA

HFD-400: Carol Pamer, Safety Evaluator, OPDRA

Electronic only cc:

HFD-002: Murray Lumpkin, Deputy Center Director for Review Management

HFD-400: Peter Honig, Director, OPDRA

HFD-040: Patricia Staub, Senior Regulatory Review Officer, DDMAC

HFD-430: Patrick Guinn, Project Manager, OPDRA

HFD-400: Sammie Beam, Project Manager, OPDRA

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<sup>i</sup> Draft package insert, February 2000.

<sup>ii</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

<sup>iii</sup> American Drug index, 42<sup>nd</sup> Edition, 1999, Facts and Comparisons, St. Louis, MO.

<sup>iv</sup> Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

<sup>v</sup> COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00; and online version of the FDA Orange Book.

<sup>vi</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>vii</sup> USP 24/NF 19. U.S. Pharmacopeia and National Formulary, 1999. The United States Pharmacopeial Convention, Inc, Rockville, MD, p. 2110-2111, "Pharmaceutical dosage forms: Capsules".

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MEMORANDUM

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
 CENTER FOR DRUG EVALUATION AND RESEARCH  
 FOOD AND DRUG ADMINISTRATION  
 DEPARTMENT OF HEALTH AND HUMAN SERVICES

DATE: April 25, 2000  
 TO: Mehul Mehta, Ph.D.  
 THROUGH: Raman Baweja, Ph.D.  
 FROM: Vanitha J. Sekar, Ph.D.  
 SUBJECT: Pre-45 Day Filing Meeting for NDA 21-235  
 Prozac® (Fluoxetine) 90 mg \_\_\_\_\_ capsules  
 Date of Filing Meeting: 5-12-2000

Eli Lilly and Company is requesting approval of a \_\_\_\_\_ enteric coated pellet formulation of fluoxetine HCl (Prozac®) containing the equivalent of 90 mg fluoxetine (to be dosed once weekly) as enteric coated pellets for the treatment of depression, \_\_\_\_\_ and \_\_\_\_\_

**Studies supporting Section 6 of the NDA:** The Clinical Pharmacology/Biopharmaceutics Section of the NDA contains results from four studies. Of these, 2 are clinical pharmacology studies in healthy volunteers: 1) Bioequivalence study (with food effect component) comparing the proposed modified release formulation to the current immediate release formulation and 2) Multiple dose pharmacokinetics of the 90 mg dose of enteric coated fluoxetine given once weekly. The other 2 studies are clinical efficacy, safety and adherence studies in which plasma fluoxetine concentrations were measured in patients. The data from these four studies provide the basis for the characterization of the performance of the 90 mg enteric coated pellet formulation. The sponsor has also provided dissolution specifications for this modified release formulation.

**Recommendation:** Based on the information provided, the Office of Clinical Pharmacology and Biopharmaceutics finds the submission fileable. Expected time of completion of the review is end of September 2000.

[ *LSI* ] 4/25/00

Vanitha J. Sekar, Ph.D.  
 Reviewer  
 Neuropharmacological Drug Products (DPE-1)

[ *LSI* ] 4/26/00

Raman Baweja, Ph.D.  
 Team Leader  
 Neuropharmacological Drug Products (DPE-1)

[ *LSI* ] 4/26/00

Mehul Mehta, Ph.D.  
 Director  
 Division for Pharmaceutical Evaluation-1

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DAVID

NDA 21-235

MAR 20 2000

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Prozac (fluoxetine hydrochloride) 90 mg Capsules

Therapeutic Classification: Standard (S)

Date of Application: March 13, 2000

Date of Receipt: March 14, 2000

Our Reference Number: NDA 21-235

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 13, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 14, 2001 and the secondary user fee goal date will be March 14, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action

is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing.

FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

[Signature] 3/26/80

John S. Purvis  
Chief, Project Management Staff  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-235

HFD-120/Div. Files

HFD-120/P.David

HFD-120/RKatz/TLaughren/AMosholder

HFD-120/GFitzgerald

HFD-120/RSeEVERS/GGill-Sangha

HFD-860/RBaweja

HFD-710/KJin

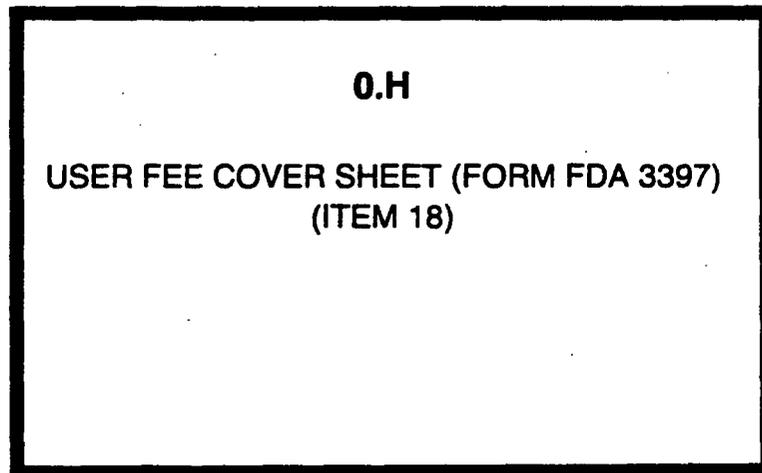
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		USER FEE COVER SHEET Expiration Date: 04-30-01	
See Instructions on Reverse Before Completing This Form			
1. APPLICANT'S NAME AND ADDRESS  Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285  c/o Gregory T. Brophy, Ph.D. Director U.S. Regulatory Affairs		2. PRODUCT NAME Procaine	
2. TELEPHONE NUMBER (include Area Code) (317) 277-3799		3. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO (APPLICATION NO. CONTAINING THE DATA).	
4. USER FEE I.D. NUMBER 3902		5. LICENSE NUMBER / NDA NUMBER 21-235	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION			
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/82 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN DRUG AND COSMETIC ACT EXCEPTION UNDER SECTION 738(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.) <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 738(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.) <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)			
<b>FOR BIOLOGICAL PRODUCTS ONLY</b>			
<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION <input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY <input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT <input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 361 OF THE FDS ACT <input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/82			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input type="checkbox"/> NO (See reverse side if answered YES)			
A completed form must be signed and accompany each new drug or biologic product application and each new Supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.			
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:  DHHS, Reports Clearance Officer, Paperwork Reduction Project (0910-0297) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W Washington, DC 20201			
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.  Please DO NOT RETURN this form to this address.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Gregory T. Brophy, Ph.D. Director U.S. Regulatory Affairs	DATE March 13, 2000

FORM FDA 357 (2-99)

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**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** February 22 , 2000

**FROM:** Thomas P. Laughren, M.D. [ 151 ]  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approval Action for Prozac Weekly (fluoxetine)  
for the longer-term treatment of depression

**TO:** File NDA 21-235  
[Note: This overview should be filed with the 1-15-01 response to the 1-8-01  
approvable letter for this NDA.]

NDA 21-235 provides data in support of a claim for longer-term treatment with a new fluoxetine 90 mg capsule that is intended for once weekly administration in depressed patients who have responded to fluoxetine 20 mg/day for an acute episode of depression. We issued an approvable letter 1-8-01, and Lilly responded with a 1-15-01 amendment. This amendment included minor changes to labeling, which Dr. Mosholder, who is now the assigned medical officer for this NDA, found acceptable (see 2-2-01 review). The proposed modifications by Lilly were also deemed acceptable by Dr. Sekar from OCPB. We reached agreement with Lilly on 2-2-01 on the final version of labeling that is included in the approval package.

However, Dr. Mosholder, in a 2-21-01 addendum to his 2-2-01 review, has now clarified that he agrees with Dr. Kathy Smith, the original medical officer who was assigned to this NDA. She recommended against the approval of this application, and Dr. Mosholder also recommends against approval. His reasons are identical to Dr. Smith's reasons: (1) study HCIZ did not show superiority of Prozac Weekly over placebo at a 0.05 level on the protocol specified endpoint, i.e., rate of relapse at 16 weeks, and (2) study HCIZ did not establish the noninferiority of Prozac Weekly to Prozac 20 mg qd.

I explained my disagreement with Dr. Smith in my 12-16-00 memo, and the basis for my disagreement with Dr. Mosholder is identical. Nevertheless, I will briefly summarize my views again here.

It is true that study HCIZ did not succeed on the protocol specified primary outcomes at 16 weeks, i.e., superiority of fluoxetine 90 mg qwk vs placebo on rate of relapse and noninferiority of fluoxetine 90 mg qwk vs fluoxetine 20 mg qd on rate of relapse. Nevertheless, both Drs. Smith and Siddiqui, the biometrics reviewer, agreed that the sponsor demonstrated a benefit over placebo for continuation or maintenance treatment with fluoxetine 90 mg qwk, according to the usual standard for a trial of this design, i.e., statistical significance for time to relapse. Fluoxetine 90 mg qwk was superior to placebo on rate of relapse at week 25 and on most secondary outcomes. Regarding the comparison with fluoxetine 20 mg qd, fluoxetine 90 mg qwk generally met the test for noninferiority for the first 12 weeks of observation, but appeared not to be as effective as fluoxetine 20 mg qd beyond 12 weeks. Dr. Siddiqui concluded that these data support the sponsor's claim of longer-term efficacy of fluoxetine 90 mg qwk vs placebo, but not the claim of noninferiority to fluoxetine 20 mg qd. As noted, Drs. Smith and Mosholder recommended against an approval of this NDA, on the grounds that the primary purpose of this new formulation and treatment strategy was to provide an equivalent substitute for fluoxetine 20 mg qd, and it fails this test.

While study HCIZ did not succeed on the protocol specified primary outcomes, I think it does demonstrate superiority of fluoxetine 90 mg qwk over placebo for continuation/maintenance treatment of depression. The standard of noninferiority to fluoxetine 20 mg qd is not, in my view, a reasonable requirement, and in fact cannot, in my view, be a requirement under the law. The FD&C Act does not require that a proposed treatment be as good as another treatment, but rather, that it be shown to be effective in adequate and well-controlled trials. I think study HCIZ meets that rather minimal standard for fluoxetine 90 mg qwk. Thus, I disagree with Drs. Smith and Mosholder. I think this NDA can be approved, and that the issue of the comparison of fluoxetine 90 mg qwk to fluoxetine 20 mg qd can be handled in labeling. I believe that the agreed upon labeling adequately cautions the prescriber that equivalence with Prozac 20 mg qd has not been established.

Even though we have gone the extra step to make this point in labeling, it is virtually always the case when we approve any drug or any new formulation of a drug that we have not shown equivalence to other drugs, or to other formulations or doses of that same drug. Thus, one virtually never knows the relative efficacy of different drugs, different formulations of the same drug, or even different doses of the same drug, since these are almost never tested in noninferiority designs. The Prozac Weekly labeling advises prescribers that "If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen." I think this advice adequately addresses the concern raised by Dr. Mosholder.

Thus, I recommend that we issue the attached approval letter with the mutually agreed upon labeling for this product.

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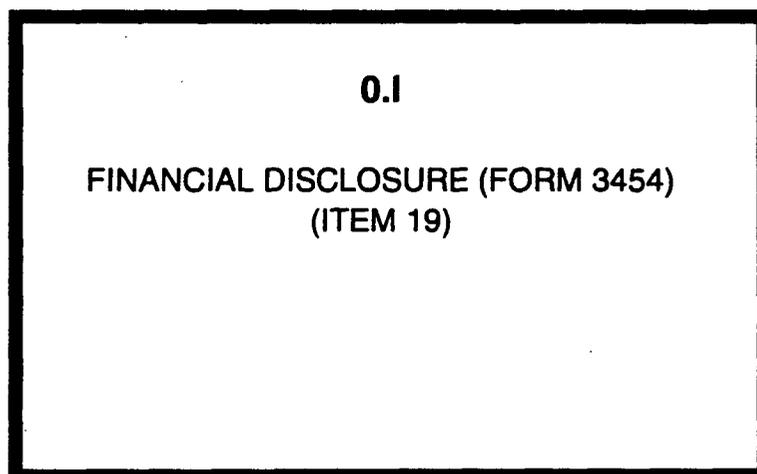
Orig NDA 21-235

HFD-120/Division File

HFD-120/TLaughren/RKatz/AMosholder/PDavid

DOC: MEMPZWKL.AP1

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Financial disclosure information was not obtained for B1Y-LC-HCIX or B1Y-LC-HCJO since both studies were clinical pharmacology studies (21 C.F.R. 54.4).

Financial disclosure information was not obtained for B1Y-MC-HCJR. This study was conducted in the United Kingdom and was not intended to prove efficacy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02
<b>CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>	

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigator	See Attached	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

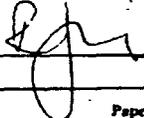
NAME <b>Rajinder Judge, M.D.</b>	TITLE <b>Medical Director</b>
FIRM/ORGANIZATION <b>Eli Lilly and Company</b>	
SIGNATURE <i>R. Judge</i>	DATE <i>9 Feb 2000</i>

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address in the right.

Department of Health and Human Services  
 Food and Drug Administration  
 5600 Fishers Lane, Room 14C-03  
 Rockville, MD 20857

**BEST POSSIBLE COPY**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration  <b>DISCLOSURE: FINANCIAL INTERESTS AND                  ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02
TO BE COMPLETED BY APPLICANT	
The following information concerning <u>see attached</u> , who participated as a clinical investigator in the submitted study <u>BIY-MC-BCIZ</u> , is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:	
Please mark the applicable checkboxes.	
<input checked="" type="checkbox"/> any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;	
<input type="checkbox"/> any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;	
<input type="checkbox"/> any proprietary interest in the product tested in the covered study held by the clinical investigator;	
<input type="checkbox"/> any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.	
Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.	
NAME <b>Rajinder Judge, M.D.</b>	TITLE <b>Medical Director</b>
FIRM/ORGANIZATION <b>Eli Lilly and Company</b>	
SIGNATURE 	DATE <b>9 Feb 00</b>
Paperwork Reduction Act Statement	
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:	
Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857	

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



NOV 19 1999

IND 53,079

Lilly Research Laboratories  
Attention: Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your Investigational New Drug Application for Prozac (fluoxetine HCl) 90 mg Delayed Release Pellets.

Reference is also made to your submission dated June 30, 1999, requesting a meeting with the Agency to discuss your proposal to further establish the safety of the excipient \_\_\_\_\_

We additionally refer to a telephone conversation dated August 18, 1999, between Mr. Paul David of this Agency and Dr. Reed Tarwater of Lilly in which we conveyed that a meeting would not be necessary since the Agency concurred with Lilly's proposal to establish the safety of \_\_\_\_\_

We acknowledge receipt of your submission dated August 20, 1999, requesting written notification that your proposal to conduct a study using \_\_\_\_\_ in addition to the other data previously supplied to the Agency would be adequate information to establish the safety of \_\_\_\_\_ for the oral use in humans.

As requested, we believe that your proposal is adequate. However, our determination of the safety for the excipient \_\_\_\_\_ would be a matter of review once we receive all of the data.

If you have any questions concerning this IND, please contact Mr. Paul David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

Russell Katz M.D.  
Acting Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**MEETING MINUTES  
IND 53,079**

**Date:** October 4, 1999; 1:30 PM  
**Location:** Conference Room E; WOC2  
**Firm:** Eli Lilly  
**Type:** Face-to-Face  
**Drug:** Prozac (fluoxetine HCL) 90 mg Delayed Release Pellets  
**Participants:**

**FDA:**

Drs. Russell Katz, Thomas Laughren, Andrew Mosholder, Rae Yuan, Vijay Tammara, Kun Jin, Ohidul Siddiqui, and Mr. Paul David

**Lilly:**

Richard Bergstrom, Ph.D. Senior Research Scientist, Pharmacokinetics  
Gregory Brophy, Ph.D. Director, US Regulatory Affairs  
Ami Claxton, Ph.D. Senior Health Outcomes Scientist  
Robert Johnston, Ph.D. Senior Statistician  
Rajinder Judge, M.D. Medical Director  
Mark Schmidt, M.D. Clinical Research Physician  
Dr. Reed Tarwater Regulatory Research Scientist  
Gary Tollefson, M.D. President, Neuroscience Products

**PURPOSE**

Lilly requested a Type B Pre-NDA meeting to discuss the clinical, statistical, and biopharmaceutics portion of this new formulation of fluoxetine HCL. The meeting request along with the briefing document were submitted to their fluoxetine \_\_\_\_\_ IND in a submission dated July 28, 1999.

**DISCUSSION**

- Lilly was previously informed, in a face to face meeting with the Agency held on July 24, 1997, that a single study demonstrating both efficacy and safety of the 90 mg formulation as a maintenance dose would be sufficient to support and NDA. They were additionally informed that they would have to demonstrate non-inferiority of fluoxetine 90 mg weekly to 20 mg daily.
- Lilly presented results from a dosing adherence study, Study HCJR, providing suggestive but not definitive evidence that adherence to once weekly dosing is at least as good as adherence to daily dosing.
- Lilly chose as their primary outcome measurement for their pivotal study, Study HCIZ, the relapse rate at week 16. This outcome measurement loses with a p value equal to 0.093. However, the p value at week 25 is 0.038. The secondary outcome

measurements, however, such as time to relapse, CGI, and HAMD demonstrate that 90 mg weekly has superior efficacy over placebo.

- Lilly also built, into study HCIZ, a rescue phase in which patients who were not doing better would be switched from either 1) placebo to 20 mg daily, 2) 20 mg daily to 40 mg daily, or 3) 90 mg weekly to 90 mg twice weekly. Although 90 mg twice weekly patients demonstrated improvement, the Agency would not be able to use these data since the design did not involve re-randomization.
- Lilly used a non-inferiority difference of 15% at week 16 between 20 mg daily versus 90 mg weekly dosing. The 20 mg daily dosing was numerically superior, and the new product failed the test. Lilly contends that a difference of 16% would have shown non-inferiority of the 90 mg weekly dose at week 16.

**Conclusions**

- Based upon the clinical data submitted in the briefing document, the Agency stated that there appears to be enough information to make a substantive review of the application, and as such, it would be fileable.
- The Agency suggested that Lilly make a case at the time of submission regarding why Study HCIZ should be considered positive since their primary outcome measurement failed, and the 90 mg delayed release weekly dosing was not shown to be non-inferior to 20 mg daily.

Minutes Preparer: LSI  
 Paul A. David, R.Ph.  
 Regulatory Project Manager, DNDP

APPEARS THIS WAY ON ORIGINAL

Chair Concurrence: LSI 10-29-99  
 (or designated signatory)

**MEETING MINUTES  
IND 53,079**

Date: April 14, 1999; 1:00 - 2:10 PM  
Location: Conference Room E; WOC2  
Firm: Eli Lilly  
Type: Face-to-Face  
Drug: Prozac (fluoxetine HCL) 90 mg Delayed Release Pellets  
Participants:  
FDA:  
Drs. Robert Seevers, Donald Klein, Glenna Fitzgerald, Barry Rosloff, John Simmons, and Mr. David

Lilly:  
Dr. Neil Anderson                      Formulation Development  
Ms. Gretchen Bowker                Regulatory Affairs (CMC)  
Ms. Jacqui Griswold                Project Manager  
Dr. Dave Hollowell                 Analytical Development  
Dr. Toby Massa                      Regulatory Affairs (CMC)  
Dr. Dave Miner                      CM&C Scientist  
Dr. Reed Tarwater                 Regulatory Research Scientist  
Dr. Ray Pohland                     Toxicology

**PURPOSE**

Lilly requested a Type B Pre-NDA meeting to discuss the toxicology and CMC of this new formulation of fluoxetine HCL. The meeting request along with the briefing document were submitted to their fluoxetine \_\_\_\_\_ IND in a submission dated March 17, 1999.

**DISCUSSION**

**Manufacturing Process**

- Lilly will provide the development history report at the time of NDA submission to assist the reviewer in understanding the manufacturing process and controls information.
- The clinical trial manufacturing lots and the primary stability lots were manufactured at the same site.
- The in-process potency assay is not, at this time, a part of the in-process controls. Lilly currently fills on weight, but they want to have the option to fill on assay value.
- The NDA should contain a complete description of the manufacturing process accompanying the manufacturing flow diagrams. The information should include the following:
  1. Coating temperature,

2. Drying temperature,
  3. Affect of temperature: stability of the excipients and the drug substance, i.e., a maximum tolerated temperature at each stage where temperature is a factor.
- Lilly will provide documentation that the \_\_\_\_\_
  - Lilly will provide the specific calculations at the time of NDA submission regarding the removal of the undersized and oversized pellets during the manufacturing of the drug product.
  - The development lots and the commercial manufacturing lots differ in the amount of significant figures used for calculating purposes. Based on the information presented in the briefing packet tables, on pages 16, 17, 19, and 21, three significant figures are used. The fill weight should be composed of two significant figures. Lilly intends to use standard operating procedures for the commercial lots.

### **Drug Product Specifications**

- The amount of fluoxetine \_\_\_\_\_ in each capsule is well below the \_\_\_\_\_ threshold based upon stability studies out to 12 months.
- Based on comparison to the fluoxetine capsule monograph and the Prozac tablet specifications, the limits of Total Impurities and Largest Individual Impurity are reasonable. However, the actual data will need to be examined.

### **Stability Data**

- Lilly will provide 18 months stability data.
- Lilly will provide the documentation of the agreement between the Agency and Lilly in August 1997 regarding the stability protocols.

### **Excipient**

- The preclinical studies conducted with \_\_\_\_\_ demonstrated no toxicology concerns since the animals did not absorb the drug. Lilly should provide documentation that this excipient, \_\_\_\_\_ used to produce their delayed release formulation is not absorbed in humans, as well.

- It was noted that \_\_\_\_\_, has never been approved in this country and, as such, the Agency treats it similar to a new drug substance.
- The DMF for the \_\_\_\_\_ excipient will be updated by June 1999. The Agency informed Lilly that we may be sending the DMF holder a deficiency letter once the updated DMF has been reviewed.

**Conclusions**

- Lilly will provide documentation regarding the stability agreement reached between the Agency and Lilly in August 1997.
- Lilly will provide the Agency with additional information regarding the \_\_\_\_\_ excipient.
- Although not part of the agenda, the Agency conveyed their concern regarding the variability of GI transit time related to diet. Since this is a once a week dosing schedule, transit time could impact on clinical effect. It was agreed that this discussion would be addressed at the clinical meeting.

Minutes Preparer:

[ P A D ]

Paul A. David, R.Ph.  
Regulatory Project Manager, DNDP

Chair Concurrence:

[ P A D ]

(or designated signatory)

APPEARS THIS WAY  
ON ORIGINAL

Attachment (copy of slides presented at meeting)

cc:

IND ORIG 53,079

IND: DIV FILE

HFD-120/RKatz/TLaughren/AMosholder

HFD-120/GFitzgerald/BRosloff

HFD-120/RSeevers/DKlein

HFD-860/CSahajwalla/RYuan

HFD-120/PDavid

HFD-810/JSimmons/CHOiberg

rd:05/03/99pd;

rev:05/20/99dk

ft:06/01/99pd

DOC #PROZAC\53079\04-14-99.MM

MEETING MINUTES

[SI] 6/22/99 [SI] 6/23/99

APPEARS THIS WAY  
ON ORIGINAL

Face-to-Face Meeting  
IND 53,079

Date: July 24, 1997; 10:00 AM  
Location: Conference Room E; WOC2  
Firm: Eli Lilly  
Drug: Prozac (fluoxetine hydrochloride) \_\_\_\_\_ Tablets  
Participants:

FDA:

Dr. Leber, Dr. Laughren, Dr. Mosholder, Dr. Choudhury, Dr. Baweja, Mr. Paul David

Lilly:

Richard F. Bergstrom, PhD, Senior Research Scientist, Pharmacokinetics,

Gary Tollefson, MD, Clinical Research Physician

Chris Bodurow, Project Manager

Robert Johnston, PhD, Statistician

Mark Schmidt, MD, Clinical Research Physician,

Reed Tarwater, PhD, Regulatory Scientist

Greg Brophy, PhD, Director, Regulatory Affairs

### Purpose

Lilly submitted correspondence dated May 22, 1997, requesting a meeting with the Agency to discuss their revised development plans for a fluoxetine 90 mg \_\_\_\_\_, once weekly dosing regimen. It was noted that the Agency held a conference call with participants from Lilly on January 13, 1997, to discuss this development plan.

### Discussion Points

- The sponsor intends to conduct a 3 arm double blinded study in which patients, who have previously responded to Prozac 20 mg daily therapy during the acute phase of the study, are treated with either Prozac 20 mg daily, Prozac 90 mg \_\_\_\_\_ tablets once weekly, or placebo.
- In model simulation pharmacokinetic studies comparing 20 mg daily versus 90 mg \_\_\_\_\_ weekly, average plasma concentrations were slightly lower for the 90 mg regimen. There is much variability, between individuals, as to plasma concentrations.
- The Agency questioned whether the sponsor intends to prove that the 90 mg \_\_\_\_\_ weekly dosing is a therapeutically exchangeable dosing regimen compared to 20-mg daily or simply an effective dosing regimen compared to placebo. Certainly, it is not a

quantitatively exchangeable regimen since patients will be receiving approximately 1/3 less drug (140 mg fluoxetine immediate release weekly versus 90 mg fluoxetine ~~—~~ weekly).

- It is the burden of the sponsor to prove that not only is this regimen an effective maintenance treatment but also that the regimen is fully exchangeable with daily dosing. Given the sponsor's proposed development plan, this would be impossible since their study design would solely prove that the weekly dosing was effective compared to placebo. If the sponsor retains their present design and the regimen is effective, the Agency would likely accept the study as sufficient evidence for efficacy. However, it is unclear at this time what type of labeling would accompany this new dosing regimen.
- As conveyed in the conference call with Lilly held on January 13, 1997, the Agency again suggested that the sponsor examine a dose other than the 90 mg dose. This may be accomplished by a twin assay study using a high and low dose for both the immediate release and the enteric coated products.
- Alternatively, the sponsor may design the study to rule out a difference in the size of the treatment effect (using a one sided approach to limits) between the new and standard dosing. This approach could persuade the Agency that the dosing regimen was exchangeable if the difference that was disproved was small enough. The test of assay sensitivity would be provided by the placebo. The sponsor replied that their current study is powered for a 25% null hypothesis of this type, and they suggested powering the study for 20%. The Agency stated that the sponsor would have to justify that a 20% would be acceptable. Additionally, an unbalanced randomization, i.e., more patients receiving drug than placebo, would be acceptable.
- A single study, distinguishing drug from placebo, would be sufficient to attain marketing of this drug.
- The Agency recommended that the sponsor submit a copy of their full protocol for review and comment prior to implementation. This submission should also include the statistical analysis plan in detail.
- The sponsor clarified that the blinding will continue for all patients who drop out of study to receive a rescue treatment.

**Decisions (agreements) reached:**

- The sponsor will consider the recommendations conveyed by the Agency for their once weekly development program.

**Unresolved issues or issues requiring further discussion:**

— None.

**Action Items:**

- The sponsor will submit a full protocol for Agency review.

Minutes Preparer:

[ 151 ]

Paul A. David , R.Ph.  
Project Manager, DNDP

Chair Concurrence:

[ 151 ]

(or designated signatory)

cc:

IND ORIG 53,079

IND: DIV FILE

151 7/29/97

HFD-120/PLeber/TLaughren/AMosholder/PDavid

HFD-710/TSahlroot/JChoudhury

HFD-860/RBaweja

rd:07/25/97pd;rev:07/29/97am

ft: 00/05/97

DOC #PROZAC\I53079\07-24-97.MM

MEETING MINUTES

APPEARS THIS WAY  
ON ORIGINAL

**NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST**

NDA <u>21-235</u> <u>3S</u>	
Drug <u>Prozac Weekly (fluoxetine HCL) Delayed</u> Release <u>90 mg Capsules</u>	Applicant <u>Lilly</u>
RPM <u>Paul David</u>	Phone <u>x4-5530</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P
Pivotal IND(s) _____	
Application classifications: Chem Class <u>3</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>1-14-01</u> Secondary <u>3-14-01</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:
  - User Fee Paid
  - User Fee Waiver (attach waiver notification letter)
  - User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
- ◆ Labeling & Labels
 

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert) .....	X
Other labeling in class (most recent 3) or class labeling.....	X
Has DDMAC reviewed the labeling? .....	<input type="checkbox"/> Yes (include review) <input checked="" type="checkbox"/> No
Immediate container and carton labels .....	X
Nomenclature review .....	X
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is  is not on the AIP.
  
- Exception for review (Center Director's memo)..... \_\_\_\_\_
- OC Clearance for approval..... \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

**APPEARS THIS WAY  
ON ORIGINAL**

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review)  Materials requested in AP letter
- ◆ Post-marketing Commitments N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- ◆ Was Press Office notified of action (for approval action only)?.....  Yes  No
  - Copy of Press Release or Talk Paper.....
- ◆ Patent X
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- ◆ Exclusivity Summary ..... X
- ◆ Debarment Statement ..... X
- ◆ Financial Disclosure X
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....
- ◆ Correspondence/Memoranda/Faxes ..... X
- ◆ Minutes of Meetings ..... X
  - Date of EOP2 Meeting 1-13-97 & 7-24-97
  - Date of pre NDA Meeting 10-4-99
  - Date of pre-AP Safety Conference \_\_\_\_\_
- ◆ Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- ◆ Federal Register Notices, DESI documents ..... N/A

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... X
- ◆ Clinical review(s) and memoranda ..... X
- ◆ Safety Update review(s) ..... N/A
- ◆ Pediatric Information Pediatric Supplement Pending
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred
- Pediatric Page..... X

Pediatric Exclusivity requested?  Denied  Granted  Not Applicable

- ◆ Statistical review(s) and memoranda ..... X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) ..... N/A  
    Recommendation for scheduling ..... \_\_\_\_\_
- ◆ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ◆ DSI Audits ..... X  
     Clinical studies  bioequivalence studies ..... \_\_\_\_\_

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**CMC INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda ..... X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ◆ DMF review(s) ..... X
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ◆ Facilities Inspection (include EES report) ..... X  
    Date completed 9-27-00 .....  Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed  Not Completed

---

**PRECLINICAL PHARM/TOX INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda ..... X
- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A
- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

APPEARS THIS WAY  
ON ORIGINAL