CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-235

ADMINISTRATIVE DOCUMENTS

0.D

PATENT STATEMENTS
(ITEM 13 AND ITEM 14)

APPEARS THIS WAY
ON ORIGINAL

ITEM 13: PATENT INFORMATION

NDA 21-235

(Prozac [redacted])

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of fluoxetine hydrochloride, as indicated. This product is the subject of this application for which approval is being sought:

Patent Number	Patent Expiry Date	Type of Patent
4,314,081	February 2, 2001	composition
5,910,319	May 29, 2017	formulation, method of use
5,985,322	May 29, 2017	method of use

The above patents are all owned by or exclusively licensed by Lilly and Company, Indianapolis, Indiana.

Feb 21, 2000

Gregory T. Brophy Ph.D.
Director, U.S. Regulatory Affairs

Date

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-235 SUPPL # _____

Trade Name Prozac Weekly (fluoxetine HCl) Delayed-Release 90 mg Capsules

Generic Name fluoxetine

Applicant Name Lilly HFD-120
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES / X / NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

      YES /___/ NO / X /

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__X__/ NO /__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /__/ NO /__X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an

esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-936 Prozac (fluoxetine HCl) Pulvules

NDA # 20-101 Prozac (fluoxetine HCl) Solution

NDA # 20-974 Prozac (fluoxetine HCl) Tablets

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability

studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_X_/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

   _____

   _____

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the

application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # B1Y-MC-HCIZ

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /X__/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 21-235 Study # B1Y-MC-HCIZ
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1_, Study # B1Y-MC-HCIZ

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named

in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 53,079 YES /X__/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____ _____
Signature of Preparer Date
Title: Regulatory Project Manager

[15] 2/26/04
_____ _____
Signature of Office of Division Director Date
Title: Division Director
cc:
Archival NDA 21-235
HFD-120/Division File
HFD-120/P.David
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

A # 21-235 (ORIGINAL NDA) Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-120 Trade and generic names/dosage form: Prozac Weekly (fluoxetine HCl) Delayed-Release 90 mg Capsules Action: AE

Applicant Lilly Therapeutic Class Antidepressant

Indication(s) previously approved Depression; once daily dosing regimen

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Proposed indication in this application Depression; once weekly dosing regimen

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___ Yes (Continue with questions) ___ No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolescents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
   - ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
   - ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
   - ___ c. The applicant has committed to doing such studies as will be required.
     - ___ (1) Studies are ongoing,
     - ___ (2) Protocols were submitted and approved.
     - ___ (3) Protocols were submitted and are under review.
     - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
   - ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes _X_No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Sponsor has a pending efficacy supplement, NDA 18-936/SE5-064, for the use of Prozac daily in depressed and OCD pediatric patients

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader).

_____ _____
Signature of Preparer and Title Date

Archival NDA # 21-235
HFD-120/Div File
NDA/PLA Action Package
HFD-104/Peds/T.Crescenzi

(revised 3/6/00)

APPEARS THIS WAY
ON ORIGINAL

0.F

DEBARMENT CERTIFICATION (ITEM 16)

APPEARS THIS WAY
ON ORIGINAL

CERTIFICATION

NDA Application No.: **21-235**

Drug Name: [ ]

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Gregory T. Brophy, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

Title: Director, U.S. Regulatory Affairs

Date: March 13, 2000

MEMORANDUM

DATE: February 22, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-235

SUBJECT: Action Memo for NDA 21-235, for the use of Prozac Weekly

NDA 21-235 was the subject of an Approvable letter dated 1/8/01. In that letter, we asked the sponsor to adopt specific labeling changes, unit of use packaging, and specific dissolution specifications.

The sponsor (Eli Lilly and Company) responded in a submission dated 1/15/01. This response has been reviewed by Dr. Andrew Mosholder, medical reviewer (reviews dated 2/2/01 and 2/21/01; Dr. Mosholder has replaced Dr. Kathy Smith as the primary medical reviewer), Dr. Sekar of the Office of Clinical Pharmacology and Biopharmaceutics (review dated 1/31/01), and Dr. Tom Laughren (memo dated 2/22/01).

Dr. Mosholder, in his review of 2/21/01, expresses his view that the application should not be approved, primarily for the same reasons as expressed originally by Dr. Smith; namely that the controlled trial performed by the sponsor did not meet its protocol specified outcome, and the trial did not demonstrate the non-inferiority of Prozac Weekly to Prozac 20 mg given daily.

Dr. Laughren, in his 2/22/01 memo, again articulates his reasons for concluding that the application should be approved. I agree. While I understand Dr. Mosholder's point of view, I do not believe that it is fundamentally different from Dr. Smith's, and I believe my memo of 1/8/01 addresses these concerns and explains why I believe the application can be approved.

Given this, and given that the sponsor has agreed to essentially all of our labeling proposals, unit of use packaging, and our proposed dissolution specifications, I will issue the attached Approval letter with the agreed-upon appended labeling.

Russell Katz, M.D.

/s/

Russell Katz
2/26/01 09:36:24 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880)** **Tracking/Action Sheet for Formal/Informal Consults**			
From: Vanitha Sekar			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: **1/31/01**	IND No.: Serial No.	NDA No. **21235**	DATE OF DOCUMENT **1/12/01**	
NAME OF DRUG **[Prozac]**	PRIORITY CONSIDERATION		Date of informal/Formal Consult **1/17/01**	
NAME OF THE SPONSOR: **[Eli Lilly]**				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2)	☐ OTHER *(SPECIFY BELOW)*:
☐ PHASE IV RELATED		[ ]

REVIEW ACTION

☒ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in meeting	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[ ]

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

The applicant's proposed labeling revisions (see attachment) are acceptable.

SIGNATURE OF REVIEWER: Vanitha J Sekar	Date 1/31/01
SIGNATURE OF TEAM LEADER:	Date
CC.: HFD # [860]; TL: [Uppoor]; DD: [Mehta]	**Project Manager:** Paul David **Date**

APPEARS THIS WAY
ON ORIGINAL

/s/

Vanitha Sekar
1/31/01 04:24:20 PM
BIOPHARMACEUTICS

Venkata Ramana Uppoor
1/31/01 04:29:13 PM
BIOPHARMACEUTICS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21235/000
Stamp: 14-MAR-2000
Regulatory Due: 14-JAN-2001
Applicant: LILLY
DRUG EPIDEMIOLOGY UNIT DROP CODE 2238
INDIANAPOLIS, IN 46285
Priority: 3S
Org Code:

Action Goal:
District Goal: 15-NOV-2000
Brand Name: PROZAC [redacted] (FLUOXETINE HCL) 90MG CA
Estab. Name:
Generic Name: FLUOXETINE HCL
Dosage Form: (DELAYED RELEASE CAPSULE)
Strength: 90 MG

FDA Contacts: P. DAVID (HFD-120) 301-594-2850 , Project Manager
G. GILL SANGHA , Review Chemist
R. SEEVERS (HFD-120) 301-594-2850 , Team Leader

Overall Recommendation: ACCEPTABLE on 27-SEP-2000 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTR OAI Status: NONE
Estab. Comment: [redacted] (on 09-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-MAR-2000				SEEVERSR
OC RECOMMENDATION	16-MAR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment: [redacted] (on 23-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-MAR-2000				GILLSANGHA
OC RECOMMENDATION	23-MAR-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment: [redacted] (on 23-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-MAR-2000				GILLSANGHA
	23-MAR-2000				

15-NOV-2000

14-JAN-2001
LILLY
3S
120
Priority:
Org Code:
Application Comment: THIS NDA IS FOR ONCE A WEEK DOSAGE OF PROZAC (on 09-MAR-2000 by G. GILL SANGHA ())

OC RECOMMENDATION ACCEPTABLE FERGUSONS
BASED ON PROFILE

Establishment: 1819470
ELI LILLY AND CO
LILLY CORP CTR/WHITE RIVER PKY/EAST DR
INDIANAPOLIS, IN 46200
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
Profile: CSN OAI Status: NONE
Estab. Comment: THIS SITE IS A BULK DS CONTROL FACILITY, AND DRUG PRODUCT MANUFACTURING, PACKAGING AND LABELING (on 20-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-MAR-2000				SEEVERSR
SUBMITTED TO DO	16-MAR-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	28-MAR-2000	PS			MROBINSO
INSPECTION PERFORMED	27-SEP-2000		17-AUG-2000		MROBINSO
PAI & GMP EI DATED 8/7-17/00 WAS NAI. THIS PLANT CONTROLS BULK ACTIVE INGREDIENTS BUT DOES NOT MAKE THEM. SITE IS NOT PROFILESD FOR (CSN).					
DO RECOMMENDATION	27-SEP-2000			ACCEPTABLE INSPECTION	MROBINSO
PAI DATED 8/7-17/00 WAS NAI.					
OC RECOMMENDATION	27-SEP-2000			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Profile: CTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-MAR-2000				DAMBROGIOJ
SUBMITTED TO DO	20-MAR-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	28-MAR-2000	PS			MROBINSO
INSPECTION PERFORMED	27-SEP-2000		17-AUG-2000		MROBINSO
PAI AND GMP EI WAS NAI.					
DO RECOMMENDATION	27-SEP-2000			ACCEPTABLE INSPECTION	MROBINSO
PAI 8/7-17/00 WAS NAI.					
OC RECOMMENDATION	27-SEP-2000			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: 1813682

ELI LILLY CO/TIPPECANOE
BOX 685 LILLY RD
LAFAYETTE, IN 47902

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: THIS SITE PERFORMS STEPS I-IV OF THE DS AND IS ALSO A BULK DS CONTROL FACILITY (on 09-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-MAR-2000				SEEVERSR
SUBMITTED TO DO	16-MAR-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	28-MAR-2000	PS			MROBINSO
INSPECTION PERFORMED	27-SEP-2000		11-AUG-2000		MROBINSO
PAI PF 21-235 WAS NAI. GMP EI OF UNRELATED API'S IS UNDER COMPLIANCE BRANCH REVIEW.					
DO RECOMMENDATION	27-SEP-2000			ACCEPTABLE INSPECTION	MROBINSO
PAI OF 21-235 WAS NAI.					
OC RECOMMENDATION	27-SEP-2000			**ACCEPTABLE** DISTRICT RECOMMENDATION	FERGUSONS

Establishment: 2618290
ELI LILLY INDUSTRIES INC
146.7 KM STATE RD NUMBER 2
MAYAGUEZ, PR 00708

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: SITE LAST INSPECTED 11/10/99 WARNING LETTER RECOMMENDED - PER FACTS. (on 16-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062) THIS SITE PERFORMS [redacted] AND ALSO DOES BULK DRUG SUSBTANCE CONTROL (on 09-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-MAR-2000				SEEVERSR
SUBMITTED TO DO	16-MAR-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	23-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	MTORRES
LAST EI WAS RE-CLASSED AS VAI BY CB.					
OC RECOMMENDATION	27-MAR-2000			**ACCEPTABLE** DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTR OAI Status: NONE
Estab. Comment: [redacted] (on 09-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-MAR-2000				SEEVERSR
OC RECOMMENDATION	16-MAR-2000			**ACCEPTABLE** BASED ON PROFILE	DAMBROGIOJ

Establishment: [redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile: CRU OAI Status: NONE

Estab. Comment: (on 13-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-MAR-2000				SEEVERSR
SUBMITTED TO DO	16-MAR-2000	GMP			EGASM
ASSIGNED INSPECTION	17-MAR-2000	GMP			EGASM
INSPECTION SCHEDULED	18-APR-2000		31-MAY-2000		IRIVERA
INSPECTION PERFORMED	15-JUN-2000		31-MAY-2000		EGASM
DO RECOMMENDATION	18-AUG-2000			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	18-AUG-2000			[redacted] DISTRICT RECOMMENDATION	EGASM

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTR OAI Status: NONE

Estab. Comment: [redacted] (on 09-MAR-2000 by G. GILL SANGHA ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-MAR-2000				SEEVERSR
OC RECOMMENDATION	16-MAR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

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MEMORANDUM

DATE: January 8, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-235

SUBJECT: Action Memo for NDA 21-235, for the use of Prozac Weekly as maintenance treatment for patients with Major Depressive Disorder (MDD)

NDA 21-235, for the use of Prozac Weekly, a 90 mg once a week delayed release dosage formulation to be used as maintenance therapy in patients with MDD who have been maintained on single daily doses of the approved Prozac dosage forms, was submitted by Eli Lilly and Company on 3/13/00. The application contains the results of a single controlled trial designed to establish the effectiveness of this dosage form in the patient population described, an additional study designed to examine the compliance with this dosage form compared to that with a single daily dose of Prozac, several biopharmaceutics studies examining the performance of this dosage form, and chemistry and manufacturing data.

The application has been reviewed by Dr. Kathy Smith, medical officer (review dated 11/9/00), Dr. Vanitha Sekar, Office of Clinical Pharmacology and Biopharmaceutics (review dated 4/25/00), Dr. Gurpreet Gill-Sangha, chemist (DMF reviews dated 3/10/00, 3/13/00, 4/3/00, 4/14/00 [2], 4/18/00, 6/20/00, 6/22/00, other CMC reviews dated 6/30/00 and 8/1/00), Dr. Robert Seevers, Chemistry Team Leader (review dated 10/12/00), Dr. Barry Rosloff, pharmacology (review dated 10/2/00), and Dr. Ohidul Siddiqui, statistician (review dated 11/17/00). Dr. Thomas Laughren, Psychiatric Drugs Team Leader, has written a comprehensive cover memo, dated 12/16/00. Dr. Smith has recommended that the application not be approved, primarily because the sponsor has not robustly demonstrated that this weekly dosage form is not "inferior" to a regimen of a single daily dose of Prozac. Dr. Laughren disagrees that this should serve as the basis for not approving the application and recommends that the application be approved.

In this memo, I will briefly review the relevant results, and provide the support for the division's decision on the application.

STUDY HCIZ

This was a randomized, parallel group, multi-center study in which patients with MDD who were stabilized on fluoxetine 20 mg once a day for 13 weeks were randomized to Prozac Weekly, 90 mg once a week, Prozac 20 mg once a day, or

placebo and followed for 25 weeks. The protocol specified 2 primary outcome measures: 1) a comparison of the rate of relapse (defined in the various reviews) between the Prozac Weekly and placebo groups at Week 16, and 2) a showing of non-inferiority of the weekly regimen compared to the daily regimen in the percentage of patients with relapse at Week 16 (defined as a showing that the weekly regimen was no more than 15% worse than the daily regimen). This latter outcome was incorporated into the protocol at the request of the division; see minutes of meetings between the sponsor and the division dated 7/24/97 and 10/4/99 (interestingly, the minutes of the 7/24/97 meeting state that a trial without the daily dosing arm would "likely" be accepted as evidence of effectiveness, while the 10/4/99 minutes state that the sponsor "would have to demonstrate" non-inferiority of the weekly regimen compared to the daily regimen to gain approval).

As described in the various reviews, 501 patients treated with daily Prozac were randomized to receive one of the 3 study treatments. The rate of relapse at Week 16 for the 3 treatment groups is given below:

	Drug-Placebo Difference In Week 16 Relapse Rate	P-value
Prozac Weekly	-.11	0.093
Prozac daily	-.18	0.003

(As reported by Dr. Smith [page 24-5], the percentage of patients Not Relapsing by Week 16 was 68%, 76%, and 58% for the Weekly, Daily, and Placebo groups, respectively.)

As pointed out by all 3 reviewers, the difference between the Prozac Weekly regimen and placebo reached nominal statistical significance at all other time points after Week 2 (including at the last 2 time points, at Weeks 22 and 25) except at Weeks 16 and 19 (see, for example, Dr. Siddiqui's Figure 3, page 5). The comparisons between Prozac daily and placebo reached nominal significance at Week 10 and until Week 25 (see Dr. Siddiqui's Figure 4, page 5).

A log-rank test of the Kaplan-Meier survival curves showed Prozac Weekly to be significantly superior to placebo (P=0.007) on Time to Relapse, though numerically inferior to the daily regimen after Week 10 (see Dr. Siddiqui's Figure 2, page 5).

In addition, nominally significant differences between the Prozac Weekly and placebo groups were seen on change from baseline in the Last Observation Carried Forward (LOCF) analyses on the protocol specified secondary measures of HAM-D core, HAM-D Subscale 5, HAM-D Anxiety Total, HAM-D Item 1, HAM-D 17, and CGI-Severity.

On the Non-Inferiority comparison to the daily regimen, the 2 regimens were shown to be "equivalent" (that is, the weekly regimen was shown to be not more than 15% worse than the daily regimen) up through Week 13, but from Week 16-25, the weekly regimen failed this test. That is, at each time point from Week 16 until the end of the study, the hypothesis that the weekly regimen was not more than 15% worse than the daily regimen could not be rejected (see Dr. Siddiqui's Figure 6, page 6).

STUDY HCJR

As Dr. Laughren describes, this was a study designed to compare compliance with the weekly and daily regimens. In this study, 109 patients with MDD who responded to Prozac 20 mg once daily for 6-16 weeks were randomized to receive either the weekly or daily regimen as in the previous study, for up to 12 weeks. Compliance was measured electronically by a chip in the cap of special pill bottles. The study was powered to assess non-inferiority of the weekly compared to the daily regimen of up to 20%. The mean adherence for the weekly regimen was 86% compared to 79% for the daily regimen; the hypothesis that the weekly regimen was not more than 20% worse than the daily regimen on this measure of compliance was rejected.

SAFETY

As Dr. Smith notes, there were no important safety issues that emerged in the experience with the Prozac Weekly dosing regimen.

Pharmacology

Dr. Rosloff notes that there is an excipient in this product [redacted] or [redacted], that is not marketed in this country. A related excipient, hydroxypropylmethylcellulose, or HPMC, is marketed in this country, and [redacted] is HPMC [redacted]

The division had asked the sponsor to address the question of whether or not the [redacted] is absorbed in the human (earlier studies had suggested that it was almost entirely eliminated in the feces in rats). We agreed that the sponsor would perform a biliary excretion study in the rat to further define whether or not the appearance of the drug in the feces was, in fact, due to its not having been absorbed.

As Dr. Rosloff describes, although there were some anomalous results in the biliary excretion study, the study suggests that [redacted] is not absorbed, nor is the [redacted] moiety absorbed. It is not known, of course, if these results generalize to humans, but this study was considered to sufficiently address the question.

CMC

As noted above, this application has been the subject of numerous CMC reviews, a number of which have resulted in interim letters. According to Dr. Seevers' review of 10/12/00, all deficiencies have been resolved.

Biopharmaceutics

The sponsor has compared the kinetics of a single dose of the 90 mg Weekly dosage form with a single dose of 90 mg given as a combination of the available 10 and 20 mg Prozac capsules; they were found to be bioequivalent. In addition, they have compared the steady state kinetics of the 90 mg Weekly dosage form with the steady state kinetics of a single daily 20 mg; here, the Weekly dosage form resulted in a Cmax which was about 81% of that achieved with the single daily dose, the average concentration with the weekly dose was about 46% of that with the daily 20 mg dose, the Cmin with the weekly dose was about 24% of that seen with the daily 20 mg dose, and the 7 day AUC with the weekly dose was about 46% of that seen with the 20 mg daily dose.

In addition, the sponsor evaluated the transition from daily dosing to weekly dosing with the proposed 90 mg form in 2 ways; first, by giving the 90 mg dose the day after the last 20 mg daily dose, and second, by giving the first 90 mg weekly dose one week after the last 20 mg daily dose. The only interesting finding was that in the former case, the Cmax following the first 90 mg dose was about 1.7 times that of the Cmax with the 20 mg daily dose at steady state.

COMMENTS

The sponsor has submitted the results of a single controlled trial designed to demonstrate the effectiveness of Prozac Weekly, a 90 mg dosage form to be given once a week to patients with MDD who have been adequately maintained on available Prozac daily dosage forms. The trial had 2 protocol specified primary goals; a showing of a statistically significant difference between drug and placebo at Week 16 in the proportion of patients experiencing a relapse, and a showing of non-inferiority at Week 16 compared to a single 20 mg dose given once a day. The study did not achieve either of these goals. For this reason, Dr. Smith has recommended that the application not be approved.

Dr. Laughren argues that the application should be considered Approvable, primarily because there is a robust finding in favor of Prozac Weekly compared to placebo on the outcome ordinarily relied upon as primary in studies of this design, Time to Relapse (p=0.007), as well as the fact that the comparisons of Prozac Weekly and placebo are significant for most other time points (except for Weeks 16 and 19) on the primary outcome of proportion of patients relapsed, and that there are nominally significant results on most of the major, standard,

secondary outcomes. Further, Dr. Laughren disagrees with Dr. Smith's insistence that the application should be approvable only if

I agree with Dr. Laughren that the study can be considered to provide evidence of the effectiveness of Prozac Weekly for these patients. While I must acknowledge that it is most unusual for us to consider a study "positive" in the face of a failure of either of the relevant contrasts on the 2 protocol specified primary endpoints to reach the traditional level of significance, I am persuaded of several points.

First, I agree with Dr. Laughren that we ought not to impose a requirement that Prozac Weekly be "equivalent" to daily administered Prozac (while I also agree that the Act does not require that "equivalence" of 2 related products be shown, I also believe that under some circumstances the Agency **might** require such a showing of "equivalence", and that the Agency does have the authority under the Act to impose this requirement). There are many examples of various versions of a drug (controlled release, parenteral, immediate release, etc.) which are approved on the basis of a showing that each individual formulation is effective, without any requirement that any two be shown to be "equivalent". While it may seem odd to have several versions of a drug available in the face of evidence that suggests that one is "less" effective than the other, certain aspects of the "less" effective formulation may compensate. In this case, for example, a once a week formulation may be more palatable for certain patients. Further, as Dr.Laughren notes, it is not immediately obvious how non-inferiority is best assessed, from a statistical point of view, in a study of this sort. This is especially true in the case of trying to demonstrate non-inferiority for the outcome measure on which we are primarily relying, Time to Relapse (see below). In any event, I believe that labeling can accurately describe the data that speaks to the comparison of interest, and the prescriber and patient can choose between the products. The primary concern, for purposes of supporting an effectiveness claim, is that the products be shown to be effective, as that term is commonly interpreted; i.e., by a showing of a significant difference between drug and an appropriate control. In my view, this dispenses with the requirement that there be statistically significant differences on two contrasts.

This takes us to the question of whether or not effectiveness, in the sense just defined, has been shown in this trial.

Here, again, I agree with Dr. Laughren. While the trial failed to meet the protocol specified endpoint, the time of the primary assessment (Week 16), as well as the endpoint itself (proportion of patients relapsing) was an odd choice for this sort of a trial, although the latter is not unreasonable in my view. As described above, the contrast on the usual primary endpoint, Time to Relapse, was highly

significant in favor of Prozac Weekly. In addition, the comparisons between Prozac Weekly and placebo on many secondary measures were nominally significant, and the protocol specified outcome was also nominally significant in favor of Prozac Weekly at most time points. For these reasons, I am persuaded that the effectiveness of Prozac Weekly has been demonstrated.

The Division had previously agreed that a single trial would be considered sufficient to gain approval for this dosage form. Ordinarily, in such a case, one would hope that that single study provide a robustly "positive" outcome; in this case, one could argue that this trial is not "robustly" positive. However, I believe that the trial is sufficiently robust to establish the product's effectiveness, especially given 1) my previously expressed view that there should rightly be only a single primary outcome measure, 2) that that measure probably should have been Time to Relapse, 3) that the sponsor's choice of primary outcome, especially the timing of the protocol specified primary contrast, was arbitrary, unusual, and not particularly appropriate from a clinical point of view, and 4) that the contrasts on the secondary measures were largely nominally significant.

There are no safety issues that would preclude approval of this product. It should be noted that one would expect that a single dose of the Prozac Weekly would be expected to yield Cmax values considerably greater than those resulting from a single 20 mg dose of Prozac (given that the Weekly dosage form is not a controlled release, but instead simply a delayed release product), and that these Cmax values would result in an increase in adverse events. However, it should be noted that this product is to be given only to those patients who have been receiving daily Prozac (20 mg) at steady state, and we have seen that the plasma levels achieved (including Cmax, Cavg, and 7 day AUC) with the Weekly formulation under these circumstances are considerably lower than with the daily Prozac 20 mg regimen (indeed, this may be an explanation of the apparent numerical superiority of the 20 mg daily regimen with continued treatment).

For these reasons, then, I will issue the attached Approvable letter, with appended draft labeling.

Russell Katz, M.D.

Cc:
NDA 21-235
HFD-120
HFD-120/Katz/Laughren/Smith/Rosloff/Gill-Sangha/Seevers/David
HFD-860/Sekar/Baweja
HFD-710/Siddiqui/Jin

/s/

Russell Katz
2/26/01 09:31:07 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

DATE: December 16 , 2000

FROM: Thomas P. Laughren, M.D. C /S/ J
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable 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 3-13-00 original submission of this NDA.]

1.0 BACKGROUND

Fluoxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, bulimia, and premenstrual dysphoric disorder (PMDD) in an immediate release capsule. Prozac (NDA 18-936) was originally approved for depression in Dec, 1987; there were subsequent approvals for OCD in Feb, 1994 and bulimia in Nov, 1996. S-058 for Sarafem (fluoxetine) was approved for PMDD in July, 2000. 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.

The studies supporting this NDA were conducted under IND 53,079, originally submitted 4-10-97. The proposed capsule includes enteric coated pellets that are intended to delay the release of fluoxetine for 1-2 hours until the pellets reach a part of the GI tract with a pH of 5.5, with the hope of better tolerability. However, Lilly has not sought any claims of improved tolerability compared to immediate release fluoxetine given on a daily basis. The primary rationale for this formulation is convenience and perhaps improved compliance, given the once weekly rather than once daily dosing. While Lilly has not sought to obtain a claim for improved compliance with this product, they have submitted data for a study in support of a claim on noninferiority to the qd regimen on an adherence outcome. The basis for believing that once weekly dosing might be sufficient is the long elimination half-life of fluoxetine and especially its active metabolite. From the initial submission,

it was clear that this new formulation was intended for maintenance treatment of patients who had already responded during daily treatment for an acute episode.

We met initially with the sponsor on 7-24-97 to discuss their development plans. In support of a claim for maintenance treatment, they intended to conduct a single trial. We agreed that a single positive trial would be sufficient. The trial they were planning included a group getting 90 mg qwk, another getting 20 mg qd, and placebo. Dr. Leber, division director at the time, noted that this was in part a question of dose response, and indicated that they would need to include a noninferiority component to the trial, i.e., both a demonstration that 90 mg qwk beats placebo, but also that 90 mg qwk is not worse than 20 mg qd by a delta of 15%.

They submitted a briefing package for a preNDA meeting on 7-28-99, including preliminary data for study HCIZ, having the design described earlier. Unfortunately, they had specified ralapse rate at 16 weeks, rather than the usual outcome of time to relapse, as the primary outcome. In fact, they had stated 2 primary hypotheses for testing, i.e., a superiority hypothesis for 90 mg qwk vs pbo, and a noninferiority hypothesis for 90 qwk vs 20 qd. Fluoxetine 90 mg qwk was not superior to placebo on this outcome (p=0.093) and was inferior to 20 mg qd (p=0.075). However, 90 qwk was superior to placebo on time to relapse and almost all other outcomes. We agreed, in a 10-4-99 preNDA meeting, that whether or not these data would support a new claim in labeling was a matter for review, and we would likely not reject such an NDA for filing.

Since the proposal involved a new formulation, it required reviews by all disciplines. CMC data were reviewed by Gurpreet Gill-Sangha, Ph.D. from the chemistry group. Pharmacology/toxicology data were reviewed by Barry rosloff, Ph.D. from the pharmacology group. Pharmacokinetic data were reviewed by Vanitha Sekarr, Ph.D. from the biopharm group. The primary review of the clinical efficacy and safety data was done by Kathy Smith, M.D. from the clinical group. Siddiqui Ohidul, Ph.D., from the Division of Biometrics, reviewed the efficacy data for study HCIZ.

The original NDA for this new formulation and claim was submitted 3-13-00. There was no safety update.

We decided not to take this NDA to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

To my knowledge there are no CMC issues precluding an approvable action for this NDA. The originally proposed name, Prozac —— had been rejected by OPDRA. However, agreement has now been reached on an alternative name, Prozac Weekly.

3.0 PHARMACOLOGY

To my knowledge there are no pharmacology/toxicology issues precluding an approvable action for this NDA.

4.0 BIOPHARMACEUTICS

To my knowledge there are no biopharmaceutics issues precluding an approvable action for this NDA. A study comparing the SD PK of this new fluoxetine 90 mg formulation with 90 mg of IR fluoxetine (HCIX) revealed a similar profile for Cmax and AUC, but as predicted, Tmax was delayed 1-2 hours fasting and ——— with food. A study comparing the steady state PK of the new 90 mg formulation given qwk with the 20 mg IR given qd (HCJO) revealed greater fluctuation in plasma concentrations for the 90 mg qwk compared to the 20 mg qd, and the mean fluoxetine and norfluoxetine plasma concentrations for the 90 mg qwk were 46% and 62% of the steady state concentrations seen with 20 mg qd.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Study HCIZ

Study HCIZ was a randomized, double-blind, parallel group, multicenter study of the relapse prevention design. There were 42 US sites. The study enrolled adult outpatients meeting DSM-IV criteria for major depression, either single episode or recurrent type. Patients were treated on an open basis with fluoxetine 20 mg qd for 13 weeks. Patients who responded during this open treatment period (response was defined as no longer meeting DSM-IV criteria for MDD and HAMD-17 total score ≤ 9 and CGI severity ≤ 2) were randomized to continuation of fluoxetine 20 mg qd, fluoxetine 90 mg qwk, or placebo. Patients were then observed for a period of up to 25 weeks. The primary outcome and comparision for this study was specified in the protocol as rate of relapse of depression at 16 weeks for fluoxetine 90 mg qwk vs placebo. A patient was classified as having relapsed if symptom criteria for a major depressive episode (DSM-IV), other than duration, were met, along with an increase in the CGI severity score of ≥ 2, for 2 or more consecutive visits, compared to the score at randomization. In addition, a patient was considered to have relapsed if there were > 6 unscheduled visits for significant emergence of symptoms, along with a HAMD-17 total score > 9 and CGI severity >2. The second protocol specified primary outcome and comparision was a noninferiority comparision on this same relapse outcome and timepoint, for fluoxetine 90 mg qwk vs fluoxetine 20 mg qd. The delta for this comparision was 15%. The primary efficacy analyses were based on the log-rank test of Kaplan-Meier survival curves. There were a number of secondary endpoints, including looking at relapse rates at other

timepoints in the 25 weeks, change from baseline on other outcomes, e.g., HAMD17, CGI, etc.

Of 1186 patients originally screened, 932 received open treatment with fluoxetine 20 mg qd, and of these, 501 met criteria for response and were randomized: fluoxetine 90 mg qwk (n=190); fluoxetine 20 mg qd (n=189); placebo (n=122). Patients were roughly 2/3 female, about 90% Caucasian, and the mean age was about 42 years. Time to relapse was significantly longer for both fluoxetine 20 mg qd ($p<0.001$) and for fluoxetine 90 mg qwk ($p<0.007$) treated patients than for placebo treated patients (p-values based on log rank test). However, rate of relapse at the primary timepoint of 16 weeks was not statistically superior for fluoxetine 90 mg qwk vs placebo ($p=0.093$). Rate of relapse was statistically superior for fluoxetine 90 mg qwk vs placebo at week 25 ($p=0.038$). On the noninferiority comparison, fluoxetine 90 mg qwk met the criterion vs fluoxetine 20 mg qd for the first 12 weeks, but consistently failed on this test from 12 to 25 weeks, including the 16 week primary timepoint. Most of the secondary analyses based on change from baseline on standard measures favored fluoxetine 90 mg qwk vs placebo.

The results were generally consistent across the centers. Results were also generally consistent for age, gender, and baseline depression scores.

5.1.2 Study HCJR

This study was designed to compare treatment adherence in patients receiving either fluoxetine 90 mg qwk or fluoxetine 20 mg qd. Depressed patients were treated on an open basis with fluoxetine for 6 to 16 weeks, and responders (n=109) were randomized to either of the above 2 treatment strategies for up to 12 weeks of continuation therapy. Adherence was assessed with electronic bottles that recorded each time the cap was removed and replaced. The noninferiority hypothesis being tested was that adherence for fluoxetine 90 mg qwk was not worse than 20% lower than for fluoxetine 20 mg qd. Mean adherence was 86% for fluoxetine 90 mg qwk compared to 79% for fluoxetine 20 mg qd. While noninferiority for this measure of adherence was demonstrated in this trial, it's not clear that this measure of adherence is adequate to support this claim. We did not have any prior discussions or agreement with the sponsor on this issue.

5.1.3 Conclusions Regarding Efficacy Data

By the sponsor's admission, this trial 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 agreed that the sponsor has 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. As noted, 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 was not as effective as fluoxetine 20 mg qd beyond 12 weeks. Dr. Siddiqui has 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. Dr. Smith has 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 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 Dr. Smith. 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 have proposed a number of changes to the sponsor's proposed labeling to fully characterize the benefits of fluoxetine 90 mg qwk vs placebo and also to note that it has not been shown to be equivalent to daily dosing with fluoxetine 20 mg. [

]

5.2 Safety Data

Dr. Smith has reviewed the relatively small amount of additional safey data for fluoxetine in 4 studies of the 90 mg dosage form. Two studies were for PK (HCIX and HCJO); one was the definitive efficacy study (HCIZ); and HCIR was designed to measure patient adherence. Overall, 292 subjects were exposed to this new formulation, amounting to approximately 71 patient-years on a qwk basis and 26 patient-years on a twice weekly basis. A fifth study, HCKN, designed to assess the safety of switching from another SSRI to fluoxetine 90 mg qwk, is ongoing. Patients were about 70% female, mostly Caucasian (94%), and the mean age was 42 years. Essentially there were no surprises and no new findings that would change our impressions about the safety of this new formulation of fluoxetine. The one finding of interest is the higher incidence of diarrhea seen in study HCIZ for fluoxetine 90 mg qwk (10%), compared to fluoxetine 20 mg qd (5%) and placebo (3%). The explanation is not clear, however, it may be a result of the new excipient used in the enteric coating for this new formulation. In any case, it should be mentioned in labeling.

5.3 Clinical Sections of Labeling

As noted, I have modified the sponsor's proposed labeling for Prozac Weekly, i.e., changes under Clinical Pharmacology (Clinical Efficacy Data), Indications and Usage, Adverse Reactions, and Dosage and Administration.

6.0 WORLD LITERATURE

I'm not aware of any literature reports pertinent to the safety of this product being submitted as part of this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, this fluoxetine 90 mg qwk formulation has not yet been approved anywhere.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

To my knowledge, 2 inspections have been completed for this NDA, one with NAI and the other with VAI ratings, both acceptable.

10.0 APPROVABLE LETTER

An approvable letter acknowledging our decision to proceed with an approval action pending agreement on labeling has been included with the approvable package.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that their new fluoxetine 90 mg formulation for once weekly administration is efficacious for the longer-term treatment of depression for patients who have responded during 20 mg qd treatment of an acute episode. [redacted]. I recommend that we issue the attached approvable letter with our proposed labeling for this product.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 21-235
HFD-120/Division File
HFD-120/TLaughren/RKatz/KSmith/AMosholder/PDavid

DOC: MEMPZWKL.AE1

APPEARS THIS WAY
ON ORIGINAL

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

David

Food and Drug Administration
Rockville MD 20857

[redacted]

OCT 25 2000

Dear [redacted]

Between August 15 and 31, 2000, Ms. Lisa Hayka, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol B1Y-MC-HCIZ) of the investigational drug enteric-coated fluoxetine hydrochloride, performed for Lilly Research Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your written response dated September 26, 2000, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Hayka presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. The discussion included, but was not limited to, adverse-event reporting deficiencies, recordkeeping inadequacies, and protocol violations. We wish to emphasize the following:

1. Certain adverse events for subjects 1702, 1706, 1709, 1714, 1726, 1737, 1741, 1747, and 1748 were not recorded in the adverse-events section of the case report forms. We remind you that federal regulations require an investigator to report promptly to the IRB and the sponsor all unanticipated problems associated with the drug.

2. Protocol-required termination laboratory tests (chemistry, hematology, and urinalysis) were not performed for subjects 1702, 1710, and 1718.

3. Any change made to study records should be initialed and dated by the person making the revision, with documentation of the reason(s) for such change.

We note your responses and your promise that appropriate corrections/changes have been implemented to ensure that the findings noted are not repeated in any ongoing or future studies.

Your response of September 26, 2000, will be included as a permanent part of the file with the inspection report. If information is requested from this file in accordance with the Freedom of Information Act, any materials released will include your response and related correspondence.

We appreciate the cooperation shown Investigator Hayka during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me at the address listed below.

Sincerely yours,

[/S/]

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

FEI: ————
Field Classification: VAI
Headquarters Classification: VAI
_____1)NAI
__X__2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
_____inadequate informed consent
_____inadequate drug accountability
__X__failure to adhere to protocol
__X__inadequate records
_____failure to report ADRS _____
_____other

cc:
HFA-224
HFD-132
HFC-230
HFD-120 Review Div. Dir./Katz
HFD-120 MO/Kathy Smith
HFD-120 PM/David
HFD-120 Doc. Rm. NDA #21-235
HFD- 45 r/f
HFD- 47 c/r/s GCP file #10216
HFD- 47 Lewin/Hajarian
HFR-CE650 DIB/Baumgarten
HFR-CE6520 BIMO Monitor/Yuscius
HFR-CE650 Field Investigator/Hayka

APPEARS THIS WAY
ON ORIGINAL

r/d: CL:10-19-00
reviewed:AEH:**(10/24/00)**
f/t:mb:**(10/24/00)**

o:\cl\———— Oct00 VAI.doc

Reviewer 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. This was the initial inspection of [redacted]

Forty-four (44) subjects enrolled, twenty-four (24) of whom were randomized in Study Period III. Seventeen (17) enrolled subjects were not randomized due to failure to meet randomization criteria. Ten (10) subjects completed Study Period III, and eleven (11) subjects entered the optional rescue treatment. Seventeen (17) enrolled subjects discontinued the study, for the following reasons: lack of efficacy, consent withdrawal, lost to follow-up, and three non-serious adverse events.

Records for 40 subjects were reviewed. A Form FDA 483 was issued for failure to report adverse events, protocol violations, and inadequate/inaccurate recordkeeping. Significant findings are noted in the accompanying letter to [redacted] Appropriate measures appear to have been taken to prevent future recurrence of the inspectional findings.

None of the inspectional findings adversely impact the acceptability of the data generated at this site. Data are acceptable.

Electronic Mail Message

Date: 10/19/00 7:33:00 AM
From: Jerry Phillips (PHILLIPSJ)
To: Paul David (DNPDP/ODEI) (DAVID)
Cc: Sammie Beam (BEAMS)
Cc: Martin Himmel (HIMMELM)
Subject: OPDRA CONSULT Prozac Weekly (Fluoxetine 90 mg) Capsules

Paul:

This is OPDRA's response to your 10/3/00 consult requesting a proprietary name review for "Prozac Weekly" for NDA 21-235 (Fluoxetine 90mg). OPDRA has no objection to the proprosed proprietary name of Prozac Weekly for this NDA. However, we have some reservations as discussed below.

Our major safety concern with this proposed name and formulation is the possibilty that a practitioner will dispense 90 mg of the immediate release Prozac for a weekly dose(10mg - 9 capsules every week or a combination of the 20mg and 10mg). The clinical consequences of this error would most likely not result in any serious outcomes, but would result in the patient receiving the wrong product that was intended. With this in mind, we would propose that the Division restrict the packaging of this product to a unit-of-use "blister" packages (e.g., 4's, 8's, 12's) with adequate instructions to the patient that this is a once-a-week dosage. This packaging configuration will also lessen the possibility of patients taking the 90mg capsule on a daily basis. Having package sizes of 100's, 500's, etc for this formulation may not result in the safest use of the product.

If you need further clarification, please feel free to E-mail me, since I will be on travel for the next week. Thanks.

Jerry Phillips
Associate Director, OPDRA

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

OCT 12 ...

Dear Dr. Brophy:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac ——— (fluoxetine hydrochloride) delayed release capsules.

We also refer to your submission dated September 6, 2000.

Our review of the Chemistry section of your submission is complete, and we have the following comments:

1. Your commitment to provide fluoxetine acetamide to the FDA labs is noted. However, your statement that the material is not immediately available as an established FDA sample is a concern. Please take the necessary steps to ensure the availability of this material so that the FDA Methods Validation process may be completed in a timely fashion.

2. We note the table of corrected relative retention values calculated by the USP method in response to Question 6. Please provide the table of relative retention times, calculated by the USP method, in your Methods Validation package

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,

[151]

Robert H. Seévers, 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

cc:
Archival NDA 21-235
HFD-120/Div. Files
HFD-120/P.David
HFD-120/G.Gill-Sangha
HFD-120/R.Seevers
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by:RHS /October 12, 2000

filename: 21235LTR.WPD

DISCIPLINE REVIEW LETTER (DR)

APPEARS THIS WAY
ON ORIGINAL

David

DEPARTMENT OF HEALTH & HUMAN SERVICES

DOCRm NDA 21-

Food and Drug Administration
Rockville MD 20857

SEP 26 2000

Dear Dr. [redacted]

Between July 24 and August 2, 2000, Mr. Mike M. Rashti, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol B1Y-MC-HCIZ) of the investigational drug enteric-coated fluoxetine hydrochloride, performed for Eli Lilly and Company. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your written response dated September 14, 2000, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Rashti presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. The discussion included, but was not limited to, deficiencies pertaining to delayed reporting of serious adverse events (SAEs) to the IRB, recordkeeping, and informed consent. We note your responses and your intent to assure better documentation to prevent the recurrence of these discrepancies in your ongoing and future studies.

We have additional comment regarding the informed consent used in this study, in that it did not contain an explanation of whom the subject should contact for answers to pertinent questions about the research. This information is required by part 50.25 of our regulations (copy enclosed). Please note item (a)7.

Your response of September 14, 2000, will be included as a permanent part-of the file with the inspection report. If information is requested from this file in accordance with the Freedom of Information Act, any materials released will include your response and related correspondence.

We appreciate the cooperation shown Investigator Rashti during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me at the address listed below.

Sincerely yours,

[/S/]

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Enclosure:
21 CFR 50.25

APPEARS THIS WAY
ON ORIGINAL

FEI: ———
Field Classification: VAI
Headquarters Classification: VAI
_____1)NAI
__X__2)VAI-no response required; responded to Form FDA 483
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
__X__inadequate informed consent
_____inadequate drug accountability
_____failure to adhere to protocol
__X__inadequate records
_____failure to report ADRS _____
__X__other (failure to promptly report two SAEs to the IRB)

cc:
HFA-224
HFD-132
HFC-230
HFD-120 Review Div. Dir./Katz
HFD-120 MO/K. Smith
HFD-120 PM/David
HFD-120 Doc. Rm. NDA #21-235
HFD- 45 r/f
HFD- 47 c/r/s GCP file #10162
HFD- 47 Lewin/Hajarian
HFR-CE150 DIB/Eagan
HFR-CE150 BIMO Monitor/Rashti

APPEARS THIS WAY
ON ORIGINAL

r/d: CL:09-15-00
reviewed:AEH:09-18-00
f/t:mb:(9/20/00)

o:\cl\ ——— Sep00 VAI.doc

Reviewer 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-three (43) subjects entered the study at this site, forty (40) of whom enrolled (received study drug). Seven (7) subjects completed the study. Thirty-three (33) subjects discontinued, for the following reasons: lack of efficacy (14), failure to meet entry or randomization criteria (8), consent withdrawal (4), adverse events (3, one each due to sedation, increased anxiety, nausea), protocol violations (2), loss to follow-up (1), and non-compliance (1).

Records were reviewed for ten (10) subjects. No under-reporting of adverse events was noted. A Form FDA 483 was issued for deficiencies related to serious adverse event reporting, recordkeeping, and informed consent. Significant findings are noted in the accompanying letter to the principal investigator.

Data acceptable

DEPARTMENT OF HEALTH & HUMAN SERVICES

David

Food and Drug Administration
Rockville MD 20857

SEP 13 2000

Dear Dr. . ——

Between August 14 and 18, 2000, Mr. Phillip D. Waldron representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol B1Y-MC-HCIZ) of the investigational drug fluoxetine hydrochloride, performed for Eli Lilly and Company. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Waldron during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me at the address listed below.

Sincerely yours,

[/S/]

APPEARS THIS WAY
ON ORIGINAL

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

FEI: ———
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted: None
_____inadequate informed consent
_____inadequate drug accountability
_____failure to adhere to protocol
_____inadequate records
_____failure to report ADRS _____
_____other

cc:
HFA-224
HFD-132
HFC-230
HFD-120 Review Div. Dir./Katz
HFD-120 MO/K. Smith
HFD-120 PM/David
HFD-120 Doc. Rm. NDA #21-235
HFD- 45 r/f
HFD- 47 c/r/s GCP file #10180
HFD- 47 Lewin/Hajarian
HFR-SW150 DIB/Chappell
HFR-SW1540 BIMO Monitor/Martinez
HFR-SW150 Field Investigator/Waldron

r/d: CL:09-13-00
reviewed:AEH:9/13/00
f/t:ju:9/14/00

o:\cl\ ———Sep00 NAI.doc