CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75755

BIOEQUIVALENCY REVIEW(S)

5.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:75-755 APPLICANT: Alphapharm PTY Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride Tablets, 20-mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

We acknowledge that the following dissolution testing method has been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 1000 mL of 0.1 N HCl at 37 °C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:
>
> *Not less than % of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.*

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Fluoxetine Hydrochloride Tablets
20 mg
ANDA #75-755
Reviewer: Chandra S. Chaurasia

Alphapharm PTY. Ltd.
Carole Park, Brisbane, Australia
US Agent: King & Spalding
Washington, DC 20006
Submission dates: December 01, 2000
January 24, 2001

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Review of an Amendment

I. Introduction:

Type of Submission: Amendment to Original ANDA

Contents of Submission: Single dose fasting study and dissolution data on 20-mg strength, and
Long term stability data as an Amendment submitted on January 24, 2001

II. Background:

Innovator's fluoxetine hydrochloride tablets, 10- and 20-mg, were approved on March 9, 1999. However, the company has not marketed the 20-mg tablet. Only the 10-mg tablet is on the market.

The current reference listed drugs are fluoxetine 10-mg tablet, fluoxetine 40-mg capsule and fluoxetine 20-mg/5mL oral solution.

Alphapharm had earlier submitted acceptable in vivo bioequivalence studies under fasting and non-fasting conditions on its fluoxetine hydrochloride 10-mg tablets, Lot 9D160, comparing it to Prozac® 10-mg tablets, Lot #2MY29M manufactured by Eli Lilly and Co (submission date: December 06, 1999).

In a subsequent application submitted on January 21, 2000, the firm requested for a biowaiver of in vivo bioequivalence studies on its fluoxetine hydrochloride 20-mg tablets, based the following:

1. A dose proportional formulation of its 10- and 20-mg fluoxetine tablets.

2. Comparative dissolution profiles between its fluoxetine 10- and 20-mg and Prozac® 10-mg tablets.

In addition, the firm has also filed a Citizen's Petition on February 10, 2000 requesting the Agency to provide a determination whether Prozac® 20-mg tablet (NDA 20-974) has been voluntarily withdrawn for safety and effectiveness reasons.

However, the waiver request on the 20-mg strength was denied, and the firm was

recommended of the following:

To conduct a single dose fasting comparative bioavailability study on the proposed formulation of fluoxetine hydrochloride 20-mg tablets, using Prozac® (fluoxetine hydrochloride) capsules, 20 mg as the comparator drug for the bioavailability purposes only.

"Additionally, the firm was advised that if the innovator begins to market the discontinued 20-mg tablet, the FDA may request the firm to conduct a bioequivalence study using the marketed Prozac® tablets, 20 mg to maintain the AB rating".

In the current amendment, the sponsor has submitted a single dose fasting study and dissolution data on the 20-mg fluoxetine tablets.

Financial Disclosure: Form FDA 3454 was submitted. The firm certifies that it has not entered into any financial arrangement with clinical investigators and that its certification is in compliance with 21 CFR part 54 and 54.2(d) [Vol. 4.1, pp. 18].

Protocol No. 00354: A Randomized Two-way Crossover, Single-Dose Study to Determine the Relative Bioavailability of Two Formulations of Fluoxetine Hydrochloride, 20 mg, in Normal Healthy Male Subjects under Fasting Conditions.

Study Information

STUDY FACILITY

Clinical Facility:
Principal Investigator:
Clinical Study Dates: Period I: July 22, 2000; Period II: September 17, 2000
Analytical Facility:
Analytical Section Head:
Analytical Study Dates: 10/18/00 to 11/03/00 for fluoxetine and norfluoxetine
Storage Period: 106 days for fluoxetine and norfluoxetine

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Fluoxetine Tablets	Prozac® Pulvules
Manufacturer:	Alphapharm Pty. Ltd.	Eli Lilly & Co.
Manufacture Date:	05/18/99	N/A
Expiration Date:	N/A	02/01/2003
ANDA Batch Size:		N/A
Batch/Lot Number:	9E160A	4AA03A
Potency:	98.7%	102.0%
Content Uniformity:	99.4% (RSD 2.4%)	101.7% (RSD 0.89%)
Strength:	20 mg	20 mg

Dosage Form:	Tablet	Capsule
Dose Administered:	20 mg	20 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	60 days

Randomization Scheme: **AB**: 1,4,5,6,9,10,14,16,17,19,23,24,25,28,29,30,33,35,37
BA: 2,3,7,8,11,12,13,15,18,20,21,22,26,27,31,32,34,36,38

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	38
Route of Administration:	Oral	**No. of Subjects Completing:**	35*
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	35
		No. of Subjects Statistical Analyses Performed:	35
Number of Doses:	N/A	**No. of Dropouts:**	3*
Loading Dose:	N/A	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	11

*Subject no. 9 withdrew prior to drug administration in Period II due to an adverse event. Subject 15 withdrew prior to drug administration in Period II for personal reasons. Subject 25 was dismissed prior to Period II drug administration due to noncompliance.

Blood Sampling: One x 10 mL each before dosing (0-time) and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10, 12, 16, 24, 48, 72, 96, 144, 192, 240, 480 and 648 hours after drug administration were collected in evacuated tubes containing K_3EDTA. The blood was centrifuged, and all plasma samples were stored at –20 °C, pending assay.

Dietary Restrictions: No alcohol, xanthine-containing beverages/foods for 48 hrs pre-dose and throughout sample collection period. No water 1hr before / after dosing. Fasted overnight pre-dose and 4hrs post-dose.

Activity Restrictions: Subjects were confined to the clinical facility approximately 12 hours prior to each drug administration until 24 hours after each drug administration. Subjects remained ambulatory or seated upright for the first 4 hours post-dose, except when warranted by medical events. No strenuous

activity during the housing period. Subjects returned to the clinic for blood sample collections at 48, 72, 96, 144, 192, 240, 360, 480 and 648 hours.

Drug Restrictions: No prescription or over-the-counter medication (including herbal products) for a period of 14 days preceding the study, and throughout the study period.

Study Results

1) Clinical

Adverse Events: During the study, 11 adverse events were reported by 7 of the 38 subjects. The adverse events are summarized in the table below:

Sub #	Study drug	Adverse Event	Severity	Therapy/Relationship to study drug
1	Test	Diarrhea	Mild	Three Rolaids Tablets taken/Unlikely
8	Test	Body aches/feeling flushed	Mild	No therapy required/ Unlikely
8	N/A	Elevated AST	Mild	Possibly/test repeated results normal
8	N/A	Elevated ALT	Mild	Possibly/test repeated results normal
8	N/A	Elevated LD	Mild	Possibly/test repeated results normal
9	Ref	Abdominal Pain and Diarrhea	Mild	No therapy required/Unrelated
10	Ref	Cold	Mild	No therapy required/Unrelated
25	Test	Sore throat	Mild	No therapy required/Unrelated
27	Test	Diarrhea	Mild	No therapy required /possibly
36	Ref	Depression	Mild	No therapy required/Unlikely
36	Test	Flu	Mild	No therapy required/Unrelated

Protocol Deviations: None other than minor sampling deviations.

2) Analytical (Not to be released under FOI)

Analytical Method Validation
Analytes: Fluoxetine and Norfluoxetine
Assay Method:
Matrix: plasma
Internal Standard: Loxapine

Assay Validation – Pre-Study Analyte: Fluoxetine				
QC Conc. (ng/mL)	0.05 (LLOQ)	1.0 (LQC)	10.0 (MQC)	40.0 (HQC)
Intra day Precision (%CV)	3.2	2.5	3.3	2.7
Intra day Accuracy (% accuracy)	95.0	100.1	100.7	97.4
Inter day Precision (%CV)	4.2	4.2	6.8	5.5
Inter day Accuracy (% accuracy)	100.4	104.2	99.7	99.9
Stability in Plasma				
Bench top stability at ambient temp.	Stable for 5 hours			
Autosampler stability at 5 °C	51 hours			
Freeze-Thaw Cycles	Stable after three freeze-thaw cycles			
Long-term storage at –20 °C	109 days			
Wet extract stability at 5 °C	30.7 hours			

Regression	weighted (1/x) linear regression
Linearity (range of r^2 values)	0.9997-0.9999
Linearity range (ng/mL)	7 points: 0.5, 1.0, 2.0, 5.0, 15.0, 25.0 and 50.0
Sensitivity/LOQ (ng/mL)	0.5 ng/mL
Mean % recovery	76.7% (LQC), 78.3% (MQC) and 86.3% (HQC)
Recovery of Internal Standard	87.2%
Specificity	No interfering peaks

Assay Validation – Within Study Analyte: Fluoxetine							
Calibration Curve Standard Conc. (ng/mL)	0.5	1.0	2.0	5.0	15.0	25.0	50.0
Inter day Precision (%CV)	4.3	3.4	4.3	4.5	2.7	2.5	0.4
Inter day Accuracy (% Accuracy)	93.4	104.4	97.8	106.0	99.9	98.2	100.4
r^2 value of representative calibration curve	0.9992-0.9999						
Linearity Range (ng/mL)	0.5 to 50.0						

Assay Validation – Pre-Study Analyte: Norfluoxetine				
QC Conc. (ng/mL)	0.05 (LLOQ)	1.0 (LQC)	10.0 (MQC)	40.0 (HQC)
Intra day Precision (%CV)	4.3	3.4	4.8	4.3
Intra day Accuracy (% accuracy)	107.0	92.9	95.7	99.5
Inter day Precision (%CV)	5.3	6.9	11.8	8.3
Inter day Accuracy (% accuracy)	110.2	96.9	95.4	104.7
Stability in Plasma				
Bench top stability at ambient temp.	Stable for 5 hours			
Autosampler stability at 5 °C	51 hours			
Freeze-Thaw Cycles	Stable after three freeze-thaw cycles			
Long-term storage at –20 °C	109 days			
Wet extract stability at 5 °C	30.7 hours			
Regression	weighted (1/x) linear regression			
Linearity (range of r^2 values)	0.9997-0.9999			
Linearity range (ng/mL)	7 points: 0.5, 1.0, 2.0, 5.0, 15.0, 25.0 and 50.0			
Sensitivity/LOQ (ng/mL)	0.5 ng/mL			
Mean % recovery	51.7% (LQC), 56.3% (MQC) and 63.5% (HQC)			
Recovery of Internal Standard	87.2%			
Specificity	No interfering peaks			

Assay Validation – Within Study Analyte: Norfluoxetine							
Calibration Curve Standard Conc. (ng/mL)	0.5	1.0	2.0	5.0	15.0	25.0	50.0
Inter day Precision (%CV)	6.8	5.6	5.7	6.9	5.4	4.9	1.0
Inter day Accuracy (% Accuracy)	100.6	103.9	97.4	98.0	97.0	103.5	99.3
r^2 value of representative calibration curve	0.9962-0.9999						
Linearity Range (ng/mL)	0.5 to 50.0						

Comments on Analytical Methodology:

The firm did not submit long-term frozen stability report on fluoxetine and norfluoxetine with the original application dated December 01, 2000. Upon Agency's request, the firm submitted them on January 24, 2001 as an amendment. The analytical method validation for fluoxetine and norfluoxetine is acceptable (Attachment I).

3) Pharmacokinetic and Statistical Analysis:

Mean Plasma Concentration: Table 1 and Figure 1 (fluoxetine) and Attachment II (norfluoxetine)

Pharmacokinetic Measures: Tables 2-3 (fluoxetine) and Tables 4-5 (norfluoxetine)

Table 1. Fasting Single-Dose In Vivo Bioequivalence Study #00354 Arithmetic Mean Plasma Fluoxetine Concentrations [ng/mL] (±SD) Vs. Time (N = 35)

Time (hr)	Test A	Reference B	Ratio (A/B)
0.0	0.000	0.000	-
1.0	1.256 ± 2.369	0.654 ± 0.704	1.92
2.0	3.723 ± 2.324	3.371 ± 2.397	1.10
3.0	6.662 ± 3.234	6.453 ± 3.189	1.03
4.0	8.743 ± 3.054	8.475 ± 2.752	1.03
5.0	11.08 ± 3 3.756	11.035 ± 3.325	1.00
6.0	12.086 ± 3.551	12.130 ± 3.042	1.00
8.0	12.117 ± 3.326	12.076 ± 3.081	1.00
10	10.689 ± 3.310	10.861 ± 3.180	0.98
12	10.300 ± 3.178	10.430 ± 2.937	0.99
16	8.514 ± 2.871	8.579 ± 2.274	0.99
24	6.855 ± 2.403	6.897 ± 2.297	0.99
48	4.100 ± 2.153	4.280 ± 2.029	0.96
72	2.667 ± 1.869	2.612 ± 1.823	1.02
96	1.679 ± 1.583	1.714 ± 1.542	0.98
144	0.692 ± 1.142	0.632 ± 1.113	1.09
192	0.365 ± 0.798	0.335 ± 0.889	1.09
240	0.215 ± 0.543	0.209 ± 0.597	1.03
360	0.053 ± 0.217	0.064 ± 0.279	0.83
480	0.018 ± 0.099	0.021 ± 0.122	0.86
648	0.000	0.000	-

Table 2. Fasting Single-Dose In Vivo Bioequivalence Study # #00354 Arithmetic Means (±SD) of Pharmacokinetic Parameters for Fluoxetine (N = 35)

PK Measures	Test (A)	Reference (B)
AUCt [ng•hr/mL]	580.1851 ± 350.36	558.4089 ± 352.53
AUCi [ng•hr/mL]	603.0097 ± 367.48	609.6057 ± 371.25
Cmax [ng/mL]	12.7211 ± 3.68	12.9423 ± 3.34
tmax [hr]	7.00 ± 1.9	7.14 ± 2.24
k_{el} [1/hr]	0.0231 ± 0.008	0.0229 ± 0.008
t½ [hr]	36.30 ± 20.69	36.37 ± 21.00

Table 3. Summary Statistics for Fluoxetine Single-Dose In Vivo Bioequivalence Study #00354 Under Fasting Conditions, N = 35

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (ng•hr/mL)	482.6165	481.2609	0.13467	1.00	95.0-105.9
Ln AUCi (ng•hr/mL)	523.9746	531.4071	0.11922	0.99	94.0-103.5
Ln Cmax (ng/mL)	12.2025	12.5406	0.09778	0.97	93.5-101.2

**Geometric LS mean values for ln-transformed data reported*

Table 4. Fasting Single-Dose In Vivo Bioequivalence Study # 00354 Arithmetic Means (±SD) of Pharmacokinetic Parameters for Norfluoxetine (N = 34) *

PK Measures	Test (A)	Reference (B)
AUCt [ng•hr/mL]	2351.27 ± 906.68	2328.80 ± 864.01
AUCi [ng•hr/mL]	2597.69 ± 1075.51	2582.76 ± 1025.53
Cmax [ng/mL]	9.1282 ± 2.78	9.2038 ± 2.56
tmax [hr]	65.77 ± 37.11	61.26 ± 33.28
k_{el} [1/hr]	0.0057 ± 0.0016	0.0056 ± 0.0015
t½ [hr]	131.84 ± 44.94	133.93 ± 45.28

*Subject # 4 deleted as the pre-dose level (only in the case of metabolite) was more than 5% of the Cmax for this subject (per the *BA/BE Guidance for Industry for Orally Administered Drug Products* issued on October 27, 2000).

Table 5. Summary Statistics for Norfluoxetine Single-Dose In Vivo Bioequivalence Study # 00354 Under Fasting Conditions, N = 34

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (ng•hr/mL)	2164.363	2162.310	0.06632	1.00	97.4-102.9
Ln AUCi (ng•hr/mL)	2379.829	2382.890	0.07060	1.00	97.0-102.8
Ln Cmax (ng/mL)	8.5676	8.7493	0.08964	0.98	94.4-101.6

**Geometric LS mean values for ln-transformed data reported*

Repeat Assays:

For fluoxetine: The firm reported that 7 (0.24%) samples out of 2882 were repeated due to double internal standard added, extraction error or for being below the lower limit of quantitation with dilution.

A total of 13 (0.45%) samples out of 2882 were repeated due to pharmacokinetic anomalies. Of these 9 repeat values confirmed original values, therefore, the original values were reported (Vol. 4.3, pp. 818). For the remaining 4 repeats, mean repeat values were reported per repeat samples acceptance criteria (SOP LAB105.00, Vol. 4.3, pp. 901).

Comments: On pharmacokinetic data

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, t_{max} *and* $t_{1/2}$) and confidence

intervals of log transformed AUC_t, AUC_i *and* C_{max} for fluoxetine and its metabolite norfluoxetine as calculated by the reviewer were in agreement with the values reported by the firm.

2. There were no statistically significant period effects for any of these PK measures.

3. The 90% confidence intervals for ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of %.

4. Subject # 4 showed a non-zero plasma norfluoxetine concentration of ng/mL (6.1% of the Cmax value of 11.367 ng/mL at 96-hour for this subject). Therefore, this subject was dropped for the PK data analyses of the metabolite per the *BA/BE Guidance for Industry for Orally Administered Drug Products* issued on October 27, 2000.

4) Formulations: Product formulations of 10- and 20-mg tablets are given below:

Ingredients	mg/tablet	
	10-mg strength	20-mg strength
Fluoxetine Hydrochloride USP	11.18[1]	22.36[2]
Colloidal Anhydrous Silica		
Crospovidone, BP		
Magnesium Stearate, BP		
Maize Starch, BP		
Microcrystalline Cellulose 101, BP		

[1]Equivalent to 10-mg of fluoxetine
[2]Equivalent to 20-mg of fluoxetine
*Approximate weights only, this ingredient used in the coating process
**Used in the coating process and does not appear in the final product

Comments on Formulation

1. The formulations for the 10-mg and 20-mg tablets are proportionally similar per definition 1 in *BA/BE Guidance for Industry for Orally Administered Drug Products* issued on October 27, 2000.

2. All inactive ingredients used in the test products are within the IIG range for oral route of administration (FDA Inactive Ingredient Guide, Jan. 1996)

***5)* Dissolution Testing:** At present an official compendial test for the fluoxetine hydrochloride tablets does not exist. The firm has used the following Agency's recommended method:

Medium: 0.1N HCl, 1000 mL
Apparatus: 1(basket), 100 rpm
Sampling Time: 5,10 and 15 minutes

Tolerance: NLT (Q) % in 15 minutes
Number of tablets: 12.

Table 6. *In Vitro* Dissolution Testing

Drug name: Fluoxetine Hydrochloride Tablets Dose strengths: 10 mg, Lot #9D160 and 20 mg, Lot #9E160A RLD: Prozac® Pulvules, Dose strength: 20 mg, Lot #4AA03A									
Assay methodology:									
Results of dissolution testing									
Sampling time (min)	Test product Fluoxetine HCl, Tab 20-mg, Lot #9E160A			Test product Fluoxetine HCl, Tab 10-mg, Lot #9D160			Reference product Prozac® 20-mg Pulvules Lot #4AA03A		
	Mean (%)	Range (%	%CV	Mean(%)	Range (%	%CV	Mean (%)	Range(%)	%CV
5	96		5.3	98%		1.8	30		26.5
10	100		2.4	100%		1.6	93		5.5
15	101		2.4	100%		1.5	100		0.9

Comments on Dissolution Testing:

1. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence studies.

2. The firm's dissolution method is acceptable.

6) Recommendations:

1. The firm has previously conducted acceptable fasting and post-prandial bioequivalence studies on its fluoxetine hydrochloride 10-mg tablets, Lot 9D160, comparing it to Prozac® 10-mg tablets, Lot #2MY29M manufactured by Eli Lilly & Co.

2. The single-dose fasting study conducted by Alphapharm Pty. Ltd. on its fluoxetine hydrochloride 20-mg tablets, Lot 9E160A, comparing it to Prozac® 20-mg pulvules, Lot #4AA03A has been found acceptable by the Division of Bioequivalence. The study demonstrates that Alphapharm's fluoxetine hydrochloride 20-mg tablet has comparable bioavailability to the reference product Prozac® 20-mg pulvule manufactured by Eli Lilly & Co.

3. The dissolution testing conducted by Alphapharm on its fluoxetine hydrochloride 20-mg tablets, Lot #9E160A is acceptable.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1 N HCl at 37 °C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than % of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

5. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing for the 20-mg fluoxetine hydrochloride tablets, and the application is approvable.

The firm should be informed of the above recommendations.

/S/
Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 01/31/01

RD INITIALED YHUANG
FT INITIALED YHUANG

Date: 1/31/2001

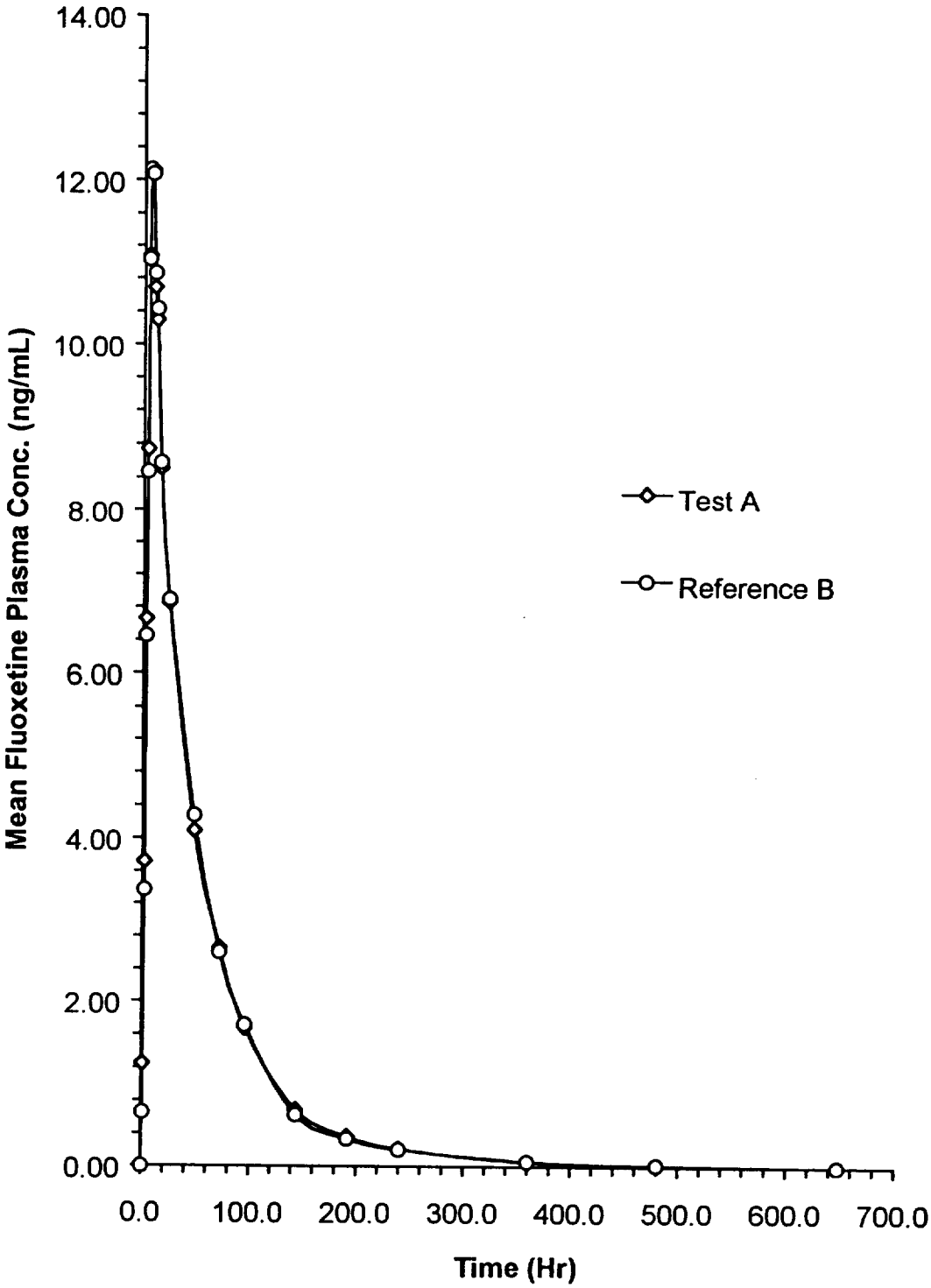
Concur: /S/

Date: 2/2/01

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA:75-755; DRUG PRODUCT: Fluoxetine Hydrochloride, 20-mg Tablets
V:\firmsam\Alphaph.arm\ltrs&rev\75755sta.d00

Fig. 1. ANDA 75-755: Fluoxetine Tab 20 mg: Fluoxetine Plasma-Concentration Time Plot (Fasting, N=35)



OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-755

SPONSOR: Alphapharm PTY. Ltd.
US Agent: King & Spalding
Washington, DC

DRUG AND DOSAGE FORM: **Fluoxetine Hydrochloride Tablets**

STRENGTH (S): **20 mg**

TYPES OF STUDIES: Fasting Bioequivalence Study on 20-mg strength

CLINICAL STUDY SITE (S)

ANALYTICAL SITE (S):

STUDY SUMMARY: Fasting Bioequivalence Study is acceptable

DISSOLUTION: Dissolution testing on 20-mg tablets is acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D. BRANCH : I

INITIAL : CS DATE : 01/31/01

TEAM LEADER : YIH-CHAIN HUANG, Ph. D. BRANCH : I

INITIAL : YHH DATE : 1/31/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 2/2/01

MAY 4

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:75-755 APPLICANT: Alphapharm PTY Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride, 10- and 20-mg Tablets

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has the following recommendations:

A. On Fluoxetine HCl 10-mg Tablets

1. No further questions at this time.

2. The following dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1 N HCl at 37 °C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than % of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

   Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

B. On Fluoxetine HCl 20-mg Tablets:

1. Your request for a biowaiver of in vivo bioequivalence studies for fluoxetine hydrochloride tablets, 20 mg is denied.

2. A single dose fasting comparative bioavailability study should be conducted on the proposed formulation of fluoxetine hydrochloride 20-mg tablets, using Prozac® (fluoxetine hydrochloride) capsules, 20 mg as the comparator drug for the bioavailability purposes only.

3. Please be advised that if the innovator begins to market the discontinued 20-mg tablet, the FDA may request you to conduct a bioequivalence study using the marketed Prozac® tablets, 20 mg to maintain the AB rating.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Fluoxetine Hydrochloride
10- and 20- mg Tablets
ANDA #75-755
Reviewer: Chandra S. Chaurasia

Alphapharm PTY. Ltd.
Carole Park, Brisbane, Australia
US Agent: Par Pharmaceutical Inc.
Spring Valley, NY
Submission dates: December 06, 1999
~~January 21, 2000~~
February 11, 2000

Review of Fasting and Post-prandial Single Dose Bioequivalence Studies (10 mg), Dissolution Data, and Waiver Request (20 mg)

I. Introduction:

Type of Submission: Original ANDA
The submission of January 21, 2000 contains the waiver request for the 20-mg strength.

Reference Listed Drug: Prozac® 10-mg (manufactured by Eli Lilly and Company, NDA 20974, March 09, 1999)

II. Background:

Indications: For the treatment of depression, obsessive-compulsive disorder, and moderate to severe bulimia nervosa.

Pharmacokinetics: Following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The elimination half-life of fluoxetine is 1 to 3 days and that of norfluoxetine is 4 to 16 days.

Available Fluoxetine Products:

Prozac® (Fluoxetine Hydrochloride) is available in the following dosage forms (per the "Electronic Orange Book"):

Capsules: 10-, 20- and 40-mg strengths
Tablets: 10-mg strength

Fluoxetine hydrochloride tablets, 10- and 20-mg, were approved on March 9, 1999. The innovator Eli Lilly and Co. has not marketed the 20-mg tablet. Only the 10-mg tablet is on the market.

III. Protocol No. 436-99-202: A 2-Way Crossover Comparative Fasting Bioavailability Study of Fluoxetine Hydrochloride 10-mg Tablets in Healthy Male Volunteers

A. Study Information

Clinical Site:

Principal Investigators:
Clinical Dates: Period I: May 22, 1999
Period II: August 7, 1999
Subjects: *Recruited:* 39 (36+3 alternates) normal healthy, non-smoking, male volunteers 20-45 years of age, weighing within 10% of their ideal weights.
Entered: 38 (subject # 16 did not show up for Period 1)
Completed: 32 (3 Asian, 3 Black, 1 East Indian, 4 Hispanic and 21 Caucasian); subjects # 8,10,11,29,32 and 35 withdrew from study.

Analytical Site:

Analytical Director:

Analysis Dates: 09/09-09/23/1999 (Vol.1.3, pp. 810)

Storage Period: Not more than 125 days at -20 ±5 °C

Study Design: Single-dose fasting, two-way crossover

Washout Period: 75 days

Products Tested

Test Product: Fluoxetine HCl Tablets, 10 mg (total dose 20 mg)
Alphapharm Pty; Lot #9D160
Manufacturing Date: April 30, 1999
Expiration Date: April 2001
Potency 98.2%
Content Uniformity 97.9%(RSD 0.93%)
Batch Size tablets

Reference Product: Prozac® Tablets, 10 mg (total dose 20 mg)
Eli Lilly & Co.; Lot #2MY29M
Expiration Date February 01, 2001

Potency 99.6%
Content Uniformity 98.6%(RSD 1.85%)

Dosing: 2x10 mg with 240-mL water. Subjects fasted overnight from 10 hours prior to and 4 hours after dosing.

Randomization: A = reference, B = test
A,B: 2,4,7,8,10,11,14,15,19,20,23,24,26,27,29,31,33,34,39,40
B,A: 1,3,5,6,9,12,13,16,17,18,21,22,25,28,30,32,35,36,37,38

Inclusion/Exclusion Criteria: Listed in Vol. 1.1, page 287-289.

Restrictions/Confinement: Listed in Vol. 1.1, page 285-289. Subjects were confined from 9:00 p.m. on the day prior to dosing and remained at the clinical site for a minimum of 24 hours after dosing, and returned to the site for subsequent blood collections.

Blood Sampling: Ten-mL each, collected using Vacutainer tubes containing EDTA prior to dosing (time 0) and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 144, 192, 240.0, 360.0, 480.0, and 648.0 hours post-dose. The plasma samples were stored at -20±5°C until analysis.

Analytical Method:
Analytes: Fluoxetine, Norfluoxetine

Specificity: No interfering peaks noted in blank chromatograms

Linearity: Correlation coefficients: Fluoxetine: 0.99836 to 0.99987 of an 8-point standard curve (0.10 to 20.0 ng/mL); Norfluoxetine: 0.99745 to 0.99984 of an 8-point standard curve (0.25 to 20.0 ng/mL).

QC Samples: *Fluoxetine*: 0.3, 6.0 and 15.0 ng/mL (CV 4.6-6.3%)
Norfluoxetine:0.75, 6.0 and 15.0 ng/mL (CV 3.9-9.2%)

LOQ: *Fluoxetine*:0.1 ng/mL (CV 6.4%)
Norfluoxetine: 0.25 ng/mL (CV 4.7%)

Accuracy:	*Fluoxetine*	*Norfluoxetine*
Intra assay:	%	%
Inter assay:	%	%

Precision:
Intra assay: % %

Inter assay: % %

Stability: *Plasma Stability:*
Bench-top: 4 hr at room temp(for both fluoxetine and norfluoxetine).
Long Term at -15 °C: 260 days (for both fluoxetine and norfluoxetine).
Freeze-thaw: three cycles (for both fluoxetine and norfluoxetine)
Processed Sample Stability (post extraction): 48 hr *at room temp* (for both fluoxetine and norfluoxetine)

Recovery: *Fluoxetine*: 0.3, 6 and 15 ng/mL: 85.5-88.8% (CV 4.0-4.8%)
Norfluoxetine: 0.75, 6.0 and 15.0 ng/mL:82.1-89.0% (CV 4.4-7.8%)
Internal Standard: Diphenhydramine: 40 ng/mL, 87.7%(CV 2.5%)

Reassays: In all, 55 out of 1485 (3.7%) and 51 out of 1485 (3.4%) samples of fluoxetine and norfluoxetine, respectively were repeated due to inconsistent internal standard response, incomplete analysis assay procedures, values below or outside accepted range, and values outside pharmacokinetic expectation.

Missing Subject Values: The following samples were not provided by the clinical site (Vol. 1.1, pp. 92-93):

Subject	Period	Time-Point	Treatment
9	2	240-hr	A
11	1	72-hr	A
22	2	240-hr	A
31	1	192-hr	A
31	1	240-hr	A
31	1	480-hr	A
9	1	360-hr	B
9	1	480-hr	B
12	1	192-hr	B
17	1	48-hr	B
27	2	480-hr	B

Comments on Analytical Results: Analytical method and data are acceptable.

B. Study Results

Clinical: Thirty-six subjects and three alternates were recruited for the study, 32 subjects completed the study.

Dropouts: Subject #16 did not show up for Period 1. Subject 35 withdrew from the study for personal reasons, at

approximately 16.5 hours after drug administration in Period 1. Subject 29 did not return for Period 2 of the study. Subject 8 withdrew prior to drug administration in Period 2 after contracting flu. Subjects 10 and 11 withdrew for personal reasons 2 and 10 days, respectively after drug administration in Period 2. Subject 32 was dismissed from the study 15 days after the drug administration in Period 2. Thus, 32 subjects completed the study. As stated by the firm, samples of subjects 11 and 32 were also analyzed because of an inadvertent mistake in sending the corresponding samples to the analytical site. Thus, the total number of subjects whose samples were analyzed by the firm for pharmacokinetic and statistical analysis was 34. However, the reviewer used data from 32 subjects (excluding subjects 11 and 32) who completed Periods 1 and 2 of the fasting study in calculating the pharmacokinetic measures.

Adverse events: Adverse events as reported (Vol. 1.1, pp. 87) by the sponsor are summarized in the following table:

Complaint	Treatment Test	Ref	Relationship to Drug /Intensity	Total # of Subjects
Headache		2	Possible/mild	2
Drowsiness	1	1	Possible/mild	2
Stiff Neck		1	Unlikely/mild	1
Tiredness	1		Possible/mild	1
Stiffness in left shoulder		1	Unrelated/mild	1
Difficulty sleeping, Paranoid, Unable to work, Manic, Feverish, Sore throat	1		Unlikely/mild	1

Protocol Deviations: None other than minor sampling deviations.

Pharmacokinetic/Statistical Analysis

The reviewer calculated pharmacokinetic measures for 32 subjects who completed the study. The values of these measures are summarized in Tables 1A-B and 2A-B, for fluoxetine and norfluoxetine, respectively. Fluoxetine and norfluoxetine plasma-concentration-time plots are given in Figures 1 and 2, respectively.

Table 1A. Mean plasma fluoxetine levels (ng/mL) versus time following an oral dose of 2x10-mg fluoxetine tablets, fasted conditions, n = 32 (excluding data from subject #11 and 32)

Time	Test (T)		Ref (R)		T/R
	Conc.	SD	Conc.	SD	
0.0	0.00	-	0.00	-	-
1.0	1.05	0.49	0.89	0.35	1.18
2.0	3.53	1.72	3.00	1.36	1.18
3.0	5.82	2.26	5.25	1.85	1.11
4.0	7.40	2.49	7.01	2.25	1.06
5.0	9.79	2.94	9.44	2.32	1.04
6.0	10.61	3.29	10.34	2.75	1.03
8.0	10.28	3.42	9.98	2.84	1.03
10.0	9.70	3.30	9.48	3.15	1.02
12.0	9.07	3.39	9.09	3.20	1.00
16.0	7.91	3.20	7.87	2.97	1.01
24.0	5.94	2.69	5.98	2.60	0.99
48.0	3.96	2.88	3.96	2.56	1.00
72.0	2.42	2.13	2.57	2.17	0.94
96.0	1.78	2.02	1.77	1.96	1.01
144.0	0.95	1.61	0.93	1.42	1.02
192.0	0.63	1.39	0.42	0.86	1.50
240.0	0.43	1.06	0.36	0.88	1.19
360.0	0.53	2.21	0.14	0.43	3.79
480.0	0.28	1.14	0.07	0.23	4.00
648.0	0.11	0.43	0.03	0.09	3.67

Table 1B. Pharmacokinetic Measures for fluoxetine following an oral dose of 2x10-mg fluoxetine tablets, fasted conditions, n = 32 (excluding data from subject #11 and 32)

PK Measures	Test ±S.D.	Reference ±S.D.	Root MSE	T/R	90% CI
AUC_t (ng*hr/mL)	694.998±870.221	593.749±530.553			
AUC_i (ng*hr/mL)	722.090±938.083	608.292±545.487			
C_{max} (ng/mL)	11.142±3.245	11.013±2.843			
t_{max} (hr)	6.53±1.57	6.91±1.80			
$t_{1/2}$ (hr)	42.85±32.22	42.28±28.46			
Ln AUC_t	6.157±0.780	6.133±0.0.669	0.1533		
Geometric mean	466.292	456.007		1.02	95.8-109.1
Ln AUC_i	6.183±0.783	6.158±0.666	0.1599		
Geometric mean	486.15	477.79		1.02	95.6-109.5
Ln C_{max}	2.368±0.301	2.364±0.276	0.1084		
Geometric mean	10.670	10.626		1.00	95.9-105.1

Table 2A. Mean plasma Norfluoxetine levels (ng/mL) versus time following an oral dose of 2x10-mg fluoxetine tablets, fasted conditions, n = 32 (excluding data from subject #11 and 32)

Time	Test (T)		Ref (R)		T/R
	Conc.	S.D.	Conc.	S.D.	
0.0	0.00	-	0.00	-	-
1.0	0.08	0.18	0.05	0.13	1.60
2.0	0.88	0.60	0.76	0.58	1.16
3.0	1.87	1.35	1.65	0.95	1.13
4.0	2.70	1.61	2.42	1.13	1.12
5.0	3.98	2.18	3.86	1.89	1.03
6.0	4.81	2.22	4.60	2.09	1.05
8.0	5.38	2.23	5.14	2.14	1.05
10.0	5.92	2.33	5.65	2.24	1.05
12.0	6.19	2.44	6.04	2.36	1.02
16.0	6.49	2.44	6.63	2.58	0.98
24.0	6.46	2.44	6.33	2.38	1.02
48.0	7.56	2.44	7.63	2.89	0.99
72.0	7.70	2.70	7.52	2.46	1.02
96.0	7.09	2.65	6.89	2.20	1.03
144.0	5.87	2.40	5.94	2.15	0.99
192.0	4.90	2.30	4.81	2.10	1.02
240.0	3.91	2.10	3.85	1.79	1.02
360.0	2.38	1.65	2.04	1.35	1.17
480.0	1.48	1.24	1.36	1.78	1.09
648.0	0.61	0.67	0.56	0.65	1.09

Table 2B. Pharmacokinetic Measures for Norfluoxetine following an oral dose of 2x10-mg fluoxetine tablets, fasted conditions, n = 32 (excluding data from subject #11 and 32)

PK Measures	Test ±S.D.	Reference ±S.D.	Root MSE	T/R	90% CI
AUC_t (ng*hr/mL)	2141.42±926.95	2109.97±885.76			
AUC_i (ng*hr/mL)	2336.90±1066.45	2301.32±1066.33			
C_{max} (ng/mL)	8.053±2.619	8.073±2.539			
t_{max} (hr)	72.21±79.80	58.78±26.83			
$t_{1/2}$ (hr)	139.25±55.21	139.05±56.44			
Ln AUC_t	7.577±0.441	7.567±0.432	0.0919		
Geometric mean	1965.08	1948.41		1.00	95.8-104.8
Ln AUC_i	7.659±0.450	7.643±0.453	0.1132		
Geometric mean	2130.30	2102.90		1.01	96.5-106.3
Ln C_{max}	2.019±0.404	2.029 ±0.375	0.0716		
Geometric mean	7.599	7.668		0.99	96.1-102.2

Comments:

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, t_{max} *and* $t_{1/2}$) and confidence intervals of AUC_t, AUC_i *and* C_{max} for fluoxetine and norfluoxetine 10-mg tablets re-calculated by the reviewer were

in agreement with the values reported by the firm.
2. There were no statistically significant period or sequence effects for any of these PK measures.
3. The 90% confidence intervals for ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

IV. Protocol No. 436-99-199: A 3-Way Crossover Comparative Food Effect Bioavailability Study of Fluoxetine Hydrochloride 10-mg Tablets in Healthy Male Volunteers

A. Study Information

Clinical Site:

Principal Investigators:

Clinical Dates: Period I: May 20, 1999
Period II: August 5, 1999
Period III: October 21, 1999

Subjects: *Recruited:* 24 normal healthy, non-smoking, male volunteers 20-45 years of age, weighing within 10% of their ideal weights.
Entered: 21 (subject # 2, 13 and 15 did not report for Period 1, Vol. 1.4, pp. 1478)
Completed: 18 (2 Asian, 1 Black, 1 East Indian, 1 Middle Eastern and 13 Caucasian); subject # 4, 14 and 23 withdrew from the study.

Analytical Site:

Analytical Director:

Analytical Dates: 11/18-11/26/1999 (Vol. 1.5, pp. 2011)

Storage Period: Not more than 191 days at -20±5 °C

Study Design: Single-dose, three-way crossover

Washout Period: 75 days

Products tested: *Lot numbers of drug products administered in this study are the same as those for the fasting study.*

Dosing: Treatment A: Test, Fasted: 2x10-mg Fluoxetine HCl tablets with 240-mL water after a supervised overnight fast.

Treatment B: Test, Fed: 2x10-mg Fluoxetine HCl tablets with 240-mL water following the consumption of a standardized breakfast.

Treatment C: Reference, Fed: 2x10-mg Prozac® tablets with 240-mL water following the consumption of a standardized breakfast.

Randomization: A = test, fasted; B = test, fed; C = reference, fed

CAB: 1,12,17,21
CBA: 2,8,14,23
BAC: 3,10,15,24
BCA: 6,9,16,22
ABC: 4,7,18,20
ACB: 5,11,13,19

Inclusion/Exclusion Criteria: Reported in the study protocol Vol. 1.4, pp. 1670.

Restrictions/Confinement: Same as reported for the fasting study, details provided in the study protocol Vol. 1.4, pp. 1670.

Blood Sampling: Ten-mL each, collected using Vacutainer tubes containing EDTA prior to dosing (time 0) and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 144.0, 192.0, 240.0, 360.0, 480.0, and 648.0 hours post-dose. The plasma samples were stored at -20 ±5°C until analysis.

B. **Analytical Method:** Same method as that used in the fasting study.

Reassays: In all, 67 out of 1169 (5.7%) and 48 out of 1169 samples (4.1%) for fluoxetine and norfluoxetine, respectively were repeated due to inconsistent internal standard response, incomplete analysis assay procedures, values below or outside accepted range, and values outside pharmacokinetic expectation.

Missing Subject Values: the clinical site did not provide the following samples:

Subject	Period	Time-Point	Treatment
6	3	240-hr	A
16	2	648-hr	A
20	1	648-hr	A
22	3	192-hr	A
22	3	240-hr	A
24	2	360-hr	A
24	2	480-hr	A
6	1	480-hr	B

16	1	240-hr	B
19	3	480-hr	B
20	2	240-hr	B
20	2	360-hr	B
24	1	480-hr	B
11	2	480-hr	C
19	3	192-hr	C
22	2	192-hr	C
22	2	240-hr	C

C. Study Results

Clinical: Number of subjects completed the study = 18

Dropouts: Twenty-four subjects were enrolled for the study. Subject # 2 (Reference, fed), 13 (Test, fasted) and 15 (Reference, fed) did not report to the clinic for Period 1. Subject # 4 (Test, fed), 14 (Test, fed), and 23 (Test, fed) withdrew from the study for personal reasons prior to drug administration in Period II. Eighteen subjects completed Periods 1,2 and 3 of the study.

Adverse events: Adverse events as reported (Vol. 1.4, pp.1489) by the sponsor are summarized in the following table:

Complaint	Treatment			Relationship to Drug /Intensity	Total # of Subjects
	Test (fast)	Test (fed)	Ref (fed)		
Numbness to left lateral tongue		1		Unrelated/mild	1
Headache	1			Unlikely/mild	1
Headache		1		Possibly/mild	1

Protocol Deviations: None other than minor sampling deviations.

Pharmacokinetic/Statistical Analysis: The firm notes that plasma samples from the 18 subjects who completed the study were analyzed, however, subject 9 was not included in the data analysis as no AUC could be calculated due to the very low levels of plasma fluoxetine and norfluoxetine concentrations in Period 2 (Treatment C: Ref, fed) and Period 3 (Treatment A: Test, fasted). Thus, data from 17 subjects were used in the PK analysis of test fed and reference fed study. In addition, as per the firm's report subject 10 ingested only one tablet (dose = 10 mg), instead of two (dose = 20 mg) in Period 2 (Treatment A: Test, fasted). The Period 2 data for subject were therefore not included in the data analyses for test fasted study. Thus, data from 16 subjects were used in the PK analysis for the test drug in Treatment A.

PK measures for fluoxetine and norfluoxetine are summarized in

Tables 3A-B, and 4A-B, respectively. Plasma-concentration-time plots are depicted in Figures 3 and 4, respectively.

Non-zero pre-dose plasma fluoxetine concentration was observed for Subject 20 in Period 3 (Ref, fed). Non-zero pre-dose norfluoxetine concentrations were observed for subject # 9 (Period 3: Test, fasted), 20 (Period 3: Ref, fed) and 21 (Period 1: Ref, fed).

The reason for the plasma non-zero pre-dose fluoxetine and/or norfluoxetine observations is not clear. However, since the washout between periods were at least 75 days, a carry-over effect seems unlikely. Additionally, the reviewer reanalyzed the data deleting subject 20 for fluoxetine, and subjects 20 and 21 for norfluoxetine. The PK measures were still within the acceptable range (please see Tables 5A-B).

Table 3A. Mean Plasma Fluoxetine levels (ng/mL) versus time following an oral dose of 2x10-mg Fluoxetine HCl tablets, fed conditions, n = 17*

Time	$Test_{fast}$* (treat A		$Test_{food}$ (treat B)		Ref_{food} (treat C)		
	Conc.	S.D.	Conc.	S.D.	Conc.	S.D.	$(Test/Ref)_{food}$
0.0	0.00	0.00	0.00	0.00	0.04	0.15	0.00
1.0	0.84	0.32	1.03	1.11	0.87	0.86	1.18
2.0	3.19	0.98	4.17	2.82	3.91	2.14	1.07
3.0	5.10	1.10	6.27	3.19	6.56	3.36	0.96
4.0	7.05	1.63	8.66	3.01	8.40	3.22	1.03
5.0	9.45	2.30	11.10	2.92	10.28	3.27	1.08
6.0	10.82	2.08	11.32	2.66	10.99	3.44	1.03
8.0	10.66	2.59	11.04	2.67	10.74	3.22	1.03
10.0	9.74	2.58	9.86	2.41	9.90	3.22	1.00
12.0	9.71	2.77	9.66	2.50	9.62	3.00	1.00
16.0	8.23	2.55	8.02	2.01	8.18	2.42	0.98
24.0	6.21	2.07	5.94	1.68	6.21	2.21	0.96
48.0	3.84	1.72	3.70	1.44	3.98	1.83	0.93
72.0	2.44	1.54	2.09	0.99	2.50	1.27	0.84
96.0	1.56	1.16	1.27	0.74	1.57	0.77	0.81
144.0	0.63	0.65	0.49	0.41	0.69	0.52	0.71
192.0	0.25	0.41	0.19	0.23	0.35	0.31	0.54
240.0	0.12	0.28	0.07	0.11	0.15	0.31	0.47
360.0	0.02	0.09	0.01	0.03	0.03	0.10	0.33
480.0	0.02	0.10	0.00	0.00	0.01	0.03	0.00
648.0	0.00	0.00	0.00	0.00	0.00	0.00	-

*data based on n = 16 for treatment A fasted study

Table 3B. Pharmacokinetic Measures for Fluoxetine following an oral dose of 2x10-mg Fluoxetine HCl tablets, fed conditions, n=17*

PK Measures	$Test_{fast}$*	$Test_{food}$	Ref_{food}	Root MSE	$(Test_{food}/Test_{fast})$	$(Test/Ref)_{food}$
AUC_t (ng*hr/mL) §	520.019 ±233.684	481.671 ±168.713	532.952 ±299.084			

AUC_i (ng*hr/mL)[§]	534.002 ±243.535	490.574 ±170.814	548.684 ±303.328			
C_{max} (ng/mL)[§]	11.300 ±2.404	11.844 ±2.790	11.556 ±3.531			
t_{max} (hr)	6.69±1.09	6.24±1.30	6.29±1.79			
$t_{1/2}$ (hr)	33.26±13.59	31.94±10.80	35.53±14.93			
Ln AUC_t	6.158±0.463	6.112±0.390	6.061±0.800	0.4092		
Geometric mean	489.164	489.432	466.986		1.00	1.05
Ln AUC_i	6.183±0.465	6.131±0.384	6.099±0.777	0.3960		
Geometric mean	501.687	499.011	484.542		0.99	1.03
Ln C_{max}	2.400±0.242	2.441±0.263	2.337±0.640	0.3952		
Geometric mean	10.712	11.429	10.299		1.07	1.11

[§]Data are arithmetic mean values(±S.D)

*data based on n=16 for treatment A fasted study

Table 4A. Mean Plasma Norfluoxetine levels (ng/mL) versus time following an oral dose of 2x10-mg Fluoxetine HCl tablets, fed conditions, n = 17*

Time	$Test_{fast}$ (treat A)		$Test_{food}$ (treat B)		Ref_{food} (treat C)		
	Conc.	SD	Conc.	SD	Conc.	SD	$(Test/Ref)_{food}$
0.0	0.00	0.00	0.00	0.00	0.73	2.33	0.00
1.0	0.00	0.00	0.06	0.16	0.88	2.62	0.07
2.0	0.77	0.41	0.90	0.65	1.74	2.67	0.52
3.0	1.52	0.64	1.67	0.86	2.55	2.21	0.65
4.0	2.46	1.00	2.83	1.23	3.57	2.37	0.79
5.0	3.79	1.66	4.28	1.74	4.62	2.33	0.93
6.0	4.97	2.02	4.99	2.18	5.37	2.33	0.93
8.0	5.55	2.05	5.70	2.24	6.11	2.45	0.93
10.0	5.94	2.10	6.18	2.42	6.49	2.50	0.95
12.0	6.51	2.05	6.88	2.60	7.03	2.45	0.98
16.0	6.97	2.21	6.97	2.35	7.11	2.34	0.98
24.0	6.83	2.04	8.80	2.06	6.91	2.06	1.27
48.0	8.82	2.57	9.01	2.54	8.50	2.30	1.06
72.0	8.63	1.93	8.73	2.71	8.22	1.73	1.06
96.0	8.24	1.99	8.16	2.60	7.57	1.94	1.08
144.0	7.03	1.70	6.53	1.97	6.39	1.86	1.02
192.0	5.55	1.83	5.24	1.77	4.83	1.70	1.08
240.0	4.28	1.77	4.19	1.84	3.89	1.89	1.08
360.0	2.32	1.26	2.13	1.24	2.12	1.35	1.00
480.0	1.87	2.50	1.50	1.86	1.20	1.02	1.25
648.0	0.78	1.09	0.60	0.99	0.50	.67	1.20

*data based on n=16 for treatment A fasted study

Table 4B. Pharmacokinetic Measures for Norfluoxetine following an oral dose of 2x10-mg Fluoxetine HCl tablets, fed conditions, n=17*

PK Measures	$Test_{fast}$	$Test_{food}$	Ref_{food}	Root MSE	$(Test_{food}/Test_{fast})$	$(Test/Ref)_{food}$
AUC_t (ng*hr/mL)[§]	2425.78	2366.85 ±922.84	2214.93 ±788.22			

	±823.66					
AUC_i (ng*hr/mL)[§]	2654.81 ±1003.41	2596.89 ±1176.24	2375.84 ±954.67			
C_{max}(ng/mL)[§]	9.413±2.223	9.396±2.669	9.269±2.149			
t_{max} (hr)	96.31±106.20	64.62±28.97	52.26±29.51			
$t_{1/2}$ (hr)	125.40±49.67	131.14±55.32	126.43 ±46.96			
Ln AUC_t	7.7393	7.6862	7.6483	0.1698		
Geometric mean	2070.81	2018.18	1952.18		0.97	1.03
Ln AUC_i	7.8215	7.7652	7.7081	0.1917		
Geometric mean	2250.50	2206.02	2083.27		0.98	1.06
Ln C_{max}	2.210±0.278	2.179±0.421	2.194±0.287	0.1217		
Geometric mean	8.1982	7.7257	7.9366		0.94	0.97

[§]Data are arithmetic mean values(±S.D)
*data based on n=16 for treatment A fasted study

Table 5A. Pharmacokinetic Measures for Fluoxetine following an oral dose of 2x10-mg Fluoxetine HCl tablets, fed conditions, (excluding subject 20).

PK Measures	$Test_{fast}$	$Test_{food}$	Ref_{food}	Root MSE	($Test_{food}$/ $Test_{fast}$)	$(Test/Ref)_{food}$
Ln AUC_t	6.161±0.479	6.127±0.397	6.240±0.529	0.2016		
Geometric mean	502.238	498.220	554.005		0.99	0.90
Ln AUC_i	6.187±0.481	6.145 ±0.392	6.240±0.529	0.2033		
Geometric mean	515.296	507.771	571.115		0.99	0.89
Ln C_{max}	2.392±0.249	2.449 ±0.270	2.485±0.202	0.1328		
Geometric mean	10.75	11.37	12.01		1.06	0.95

Table 5B. Pharmacokinetic Measures for Norfluoxetine following an oral dose of 2x10-mg Fluoxetine HCl tablets, fed conditions, (excluding subjects 20 & 21).

PK Measures	$Test_{fast}$	$Test_{food}$	Ref_{food}	Root MSE	($Test_{food}$/ $Test_{fast}$)	$(Test/Ref)_{food}$
Ln AUC_t	7.704±0.354	7.628±0.437	7.613±0.336	0.1524		
Geometric mean	2005.195	1905.862	1903.127		0.95	1.00
Ln AUC_i	7.784±0.371	7.693±0.043	7.672±0.361	0.1583		
Geometric mean	2176.050	2051.604	2024.153		0.94	1.01
Ln C_{max}	2.189±0.289	2.180±0.449	2.172±0.299	0.1239		
Geometric mean	7.984	7.714	7.760		0.97	0.99

Comments on Non-Fasting Bioequivalence Study:

1. The pharmacokinetic measures (AUC_t, AUC_i, and C_{max}) and ratios of their ln-transformed means for fluoxetine and norfluoxetine were recalculated by the reviewer. The reported values are in agreement with those obtained by the reviewer. There were no statistically significant period effects for any of these measures.

2. Ratios of means for AUC_t, AUC_i, and C_{max} of fluoxetine and norfluoxetine between test non-fasting and reference non-fasting are within the acceptable limits of 0.80-1.25.

3. There was no significant difference in the mean C_{max} values of the test fluoxetine and norfluoxetine under non-fasting conditions compared to those under the fasting conditions (Tables 4A-B). Also, there was no significant difference in the mean fluoxetine t_{max} values from the test product under fasting and non-fasting conditions. However the t_{max} value decreased by about 32 hours for the test norfluoxetine under non-fasting conditions compared with that under the fasting conditions (Table 4B).

IV. **Formulations:** Product formulations on 10- and 20-mg tablets are given below:

Ingredients	mg/tablet	
	10-mg strength	20-mg strength
Fluoxetine Hydrochloride USP	11.18[1]	22.36[2]
Colloidal Anhydrous Silica		
Crospovidone, BP		
Magnesium Stearate, BP		
Maize Starch, BP		
Microcrystalline Cellulose 101, BP		

[1]equivalent to 10-mg of fluoxetine
[2]equivalent to 20-mg of fluoxetine
*approximate weight only, this ingredient used in the coating process
**used in the coating process and does not appear in the final product

V. **Dissolution Testing:** At present an official compendial test for the fluoxetine hydrochloride tablets does not exist. The firm has used an in-house method.

Medium: 0.1N HCl, 1000 mL
Apparatus: 1(basket), 100 rpm
Sampling Time: 5,10 and 15 minutes
Tolerance (firm proposed): NLT (Q) % in 15 minutes
Number of tablets: 12.

Table 6. *In Vitro* Dissolution Testing

Drug name: Fluoxetine Hydrochloride Tablets
Dose strengths: 10 mg, Lot #9D160 and 20 mg, Lot #9E160
RLD: Prozac® tablets
Dose strength: 10 mg, Lot #2MY29M and 20-mg
Exp. 02/01/01; Test Date: 10/06/98

Method: Apparatus 1 (basket) 100 rpm, 0.1N HCl 1000 mL
Specifications (firm proposed): NLT % (Q) dissolved in 15 minutes
Assay methodology:

Results of dissolution testing

Sampling time (min)	Test product Fluoxetine HCl, Tab 10-mg, Lot #9D160			Test product Fluoxetine HCl, Tab 20-mg, Lot #9E160			Reference product Prozac® 10-mg Tablets Lot #2MY29M		
	Mean	Range	%CV	Mean	Range	%CV	Mean	Range	%CV
5	98%*	%	1.8	99%	%	5.3	99%	%	1.6
10	100%	%	1.6	101%	%	2.4	100%	%	2.0
15	100%	%	1.5	101%	%	2.4	100%	%	2.0

*Mean of 11 tablets

Comments on Dissolution Testing:

1. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence studies.
2. The Division of Bioequivalence recommends the following interim method (tentative standards obtained from NDA 20-974 Prozac® review, dated Feb 16, 1999):

   USP Apparatus 1, 100 rpm
   1000 mL 0.1 NHCl
   NLT % (Q), 15 min

VI. Waiver Request:

The firm has submitted the following to support the waiver request on its 20-mg fluoxetine hydrochloride tablets:

1. A dose proportional formulation of its 10- and 20-mg fluoxetine tablets.

2. Comparative dissolution profiles between its fluoxetine 10- and 20-mg and Prozac® 10-mg tablets.

In addition, the firm has also filed a Citizen's Petition on February 10, 2000 requesting the Agency to provide a determination whether Prozac® 20-mg tablet (NDA 20-974) has been voluntarily withdrawn for safety and effectiveness reasons.

VII. Comments on waiver request:

1. The Division of Bioequivalence has recently reviewed a controlled document OGD99221cd.699 with regards to bioequivalent requirements for fluoxetine hydrochloride 20-mg tablets (Attachment 1).
2. Currently, DBE requests bioavailability study to be conducted comparing the proposed 20-mg tablet formulation with Prozac® 20-mg capsules.
3. The dissolution testing conducted by Alphapharm on its fluoxetine hydrochloride 20-mg tablets, Lot #9E160 is acceptable. However, the firm's request for a biowaiver of in vivo bioequivalence studies for fluoxetine 20-mg tablets is denied per comment #2 above.

VIII. Recommendations:

A. On Fluoxetine HCl 10-mg Tablets

1. The single-dose fasting and limited-food bioequivalence studies conducted by Alphapharm Pty. Ltd. on its fluoxetine hydrochloride 10-mg Tablets, Lot 9D160, comparing it to Prozac® 10-mg Tablets, Lot #2MY29M have been found acceptable by the Division of Bioequivalence. These studies demonstrate that Alphapharm's fluoxetine hydrochloride 10-mg tablet is bioequivalent to the reference product Prozac® 10-mg tablet.
2. The dissolution testing conducted by Alphapharm on its fluoxetine hydrochloride 10-mg tablets, Lot #9D160 is acceptable.
3. The following dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1 N HCl at 37 °C using USP Apparatus I

(basket) at 100 rpm. The test product should meet the following specifications:

Not less than % of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing for the 10-mg fluoxetine hydrochloride tablets, and the application is approvable.

B. On Fluoxetine HCl 20-mg Tablets:

1. Firm's request for a biowaiver of in vivo bioequivalence studies for fluoxetine hydrochloride tablets, 20 mg is denied.
2. A single dose fasting comparative bioavailability study should be conducted on the proposed formulation of fluoxetine hydrochloride 20-mg tablets, using Prozac® (fluoxetine hydrochloride) capsules, 20 mg as the comparator drug for the bioavailability purposes only.
3. The firm should be advised that if the innovator begins to market the discontinued 20-mg tablet, the FDA may request the firm to conduct a bioequivalence study using the marketed Prozac® tablets, 20 mg to maintain the AB rating.

The firm should be informed of the above recommendations.

/S/

Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 4/7/00

RD INITIALED YHUANG
FT INITIALED YHUANG /S/

Date: 4/11/2000

Concur: /S/

Date: 4/13/00

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA:75-755; DRUG PRODUCT: Fluoxetine Hydrochloride, 10-mg Tablets
V:\firmsam\Alphapharm\ltrs&rev\75755sdw.d99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:75-755 APPLICANT: Alphapharm PTY Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride, 10- and 20-mg Tablets

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has the following recommendations:

A. On Fluoxetine HCl 10-mg Tablets

1. No further questions at this time.

2. The following dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1 N HCl at 37 °C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than % of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

   Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

B. On Fluoxetine HCl 20-mg Tablets:

1. Your request for a biowaiver of in vivo bioequivalence studies for fluoxetine hydrochloride tablets, 20 mg is denied.

2. A single dose fasting comparative bioavailability study should be conducted on the proposed formulation of fluoxetine hydrochloride 20-mg tablets, using Prozac® (fluoxetine hydrochloride) capsules, 20 mg as the comparator drug for the bioavailability purposes only.

3. Please be advised that if the innovator begins to market the discontinued 20-mg tablet, the FDA may request you to conduct a bioequivalence study using the marketed Prozac® tablets, 20 mg to maintain the AB rating.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-755
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)
HFD-652/CS Chaurasia CSC 4/7/00
HFD-652/YC Huang YCH 4/11/2000
HFD-617/Jennifer Pan JP 4/28/00
HFD-650/Dale Conner DC 4/20/00

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Printed in Final on 04/07/2000

BIOEQUIVALENCY - **Acceptable** Submission Dates: 12/06/1999
~~01/21/2000~~
2/11/2000

1. **FASTING STUDY** (STF) 01C **Strength: 10 mg**
Clinical Site: Outcome: **AC**

2. **FOOD STUDY** (STP) 01C **Strength: 10 mg**
Analytical Site: Outcome: **AC**

3. Dissolution Waiver DIW
~~Study Amendment~~ ~~(STA)~~ 01C **Strength: 20 mg**
(Waiver request for biostudies) Outcome: **UN**

Outcome Decisions:
AC - Acceptable **UN** - Unacceptable
NC - No Action **IC** - Incomplete

WinBio Comments:

- Fasting and limited-food studies on 10-mg tablets are acceptable.
- Dissolution data on 10- and 20-mg strengths are acceptable.
- Biowaiver on 20-mg strength is denied.

Figure 1. Mean Plasma Fluoxetine Concentration-Time Plot: Fasting Study, N=32

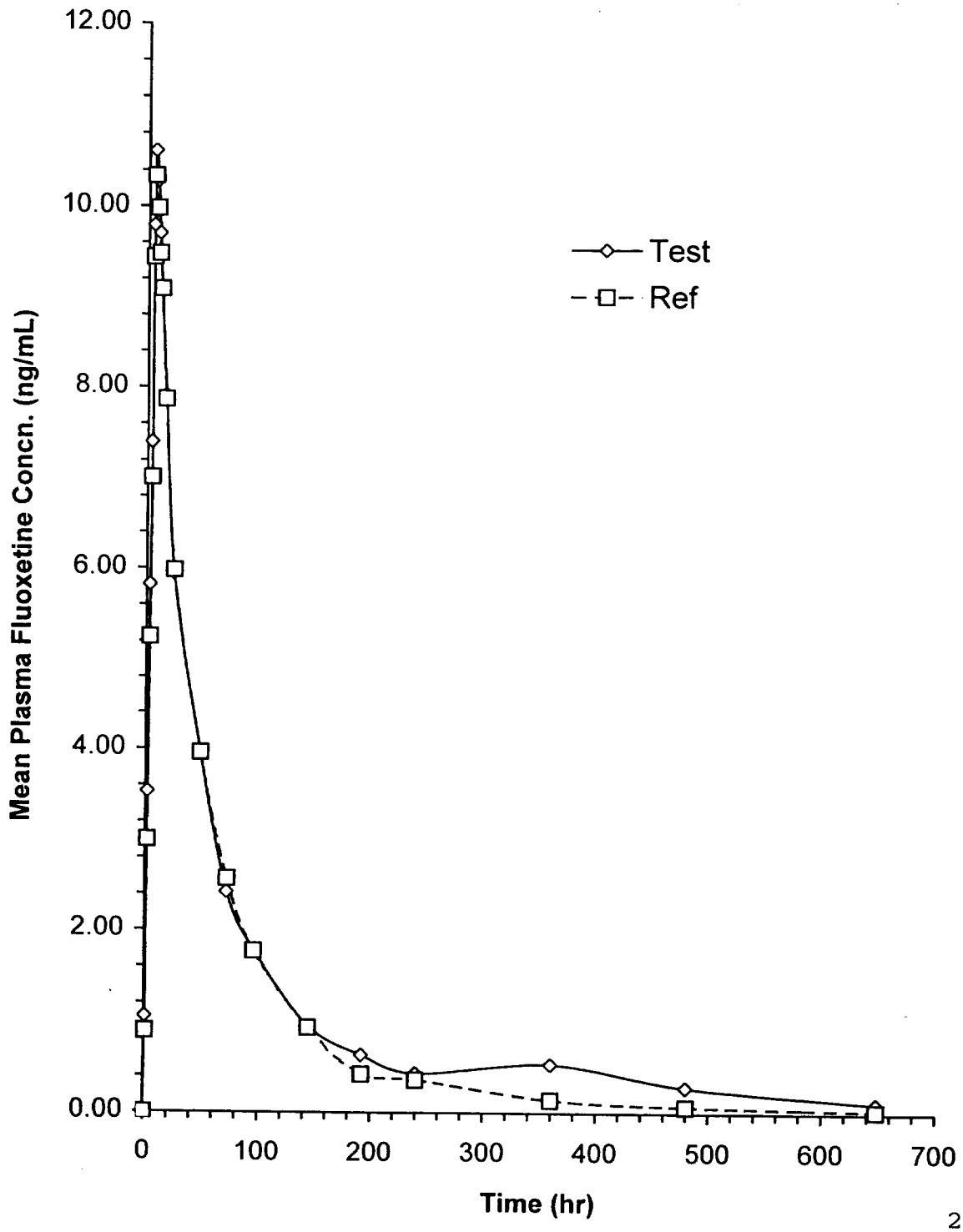

Figure 2. Mean Plasma Norfluoxetine Concentration-Time Plot: Fasting Study, N=32

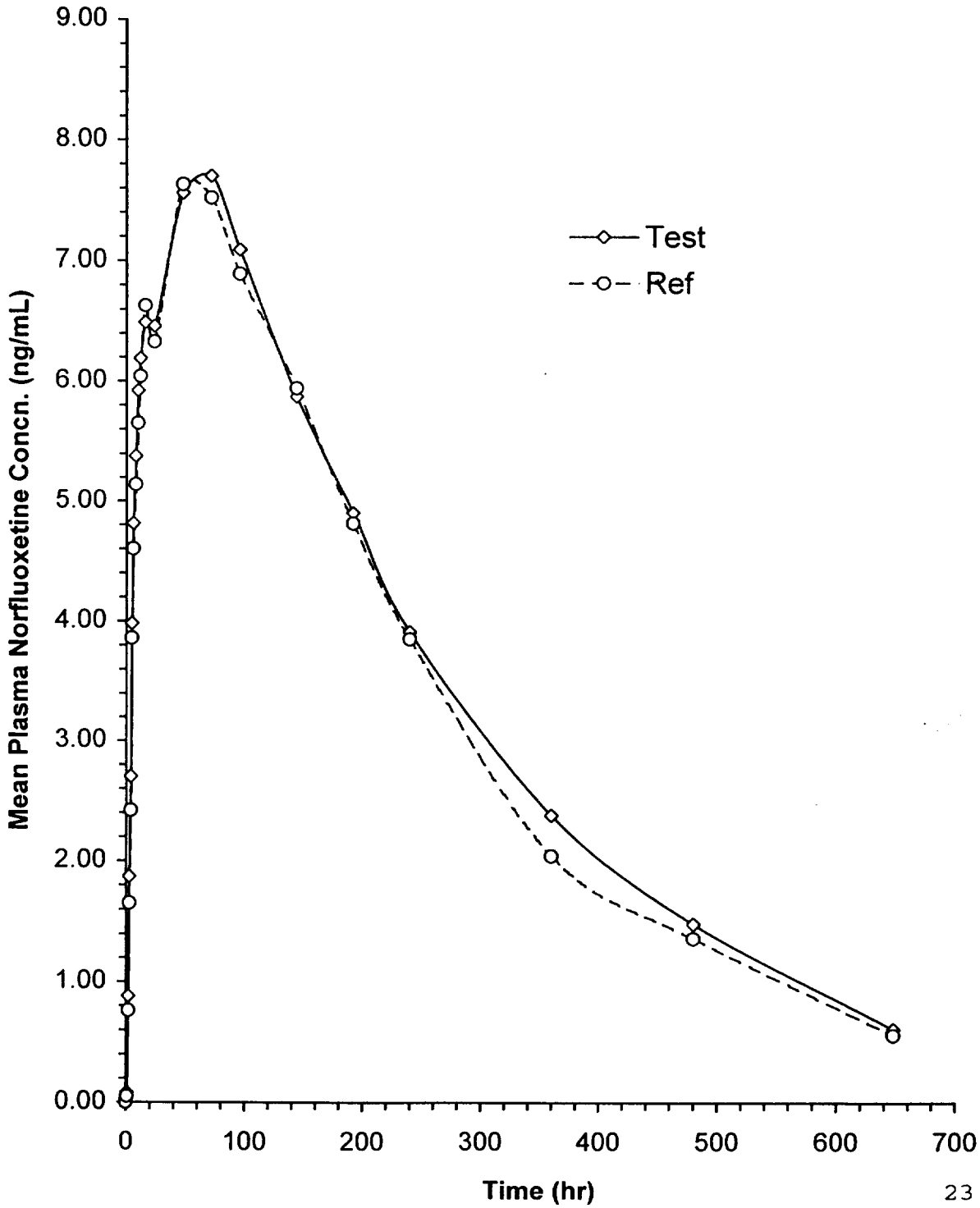

Figure 3. Mean Plasma Fluoxetine Concentration-Time Plot: Fed Study, N=17

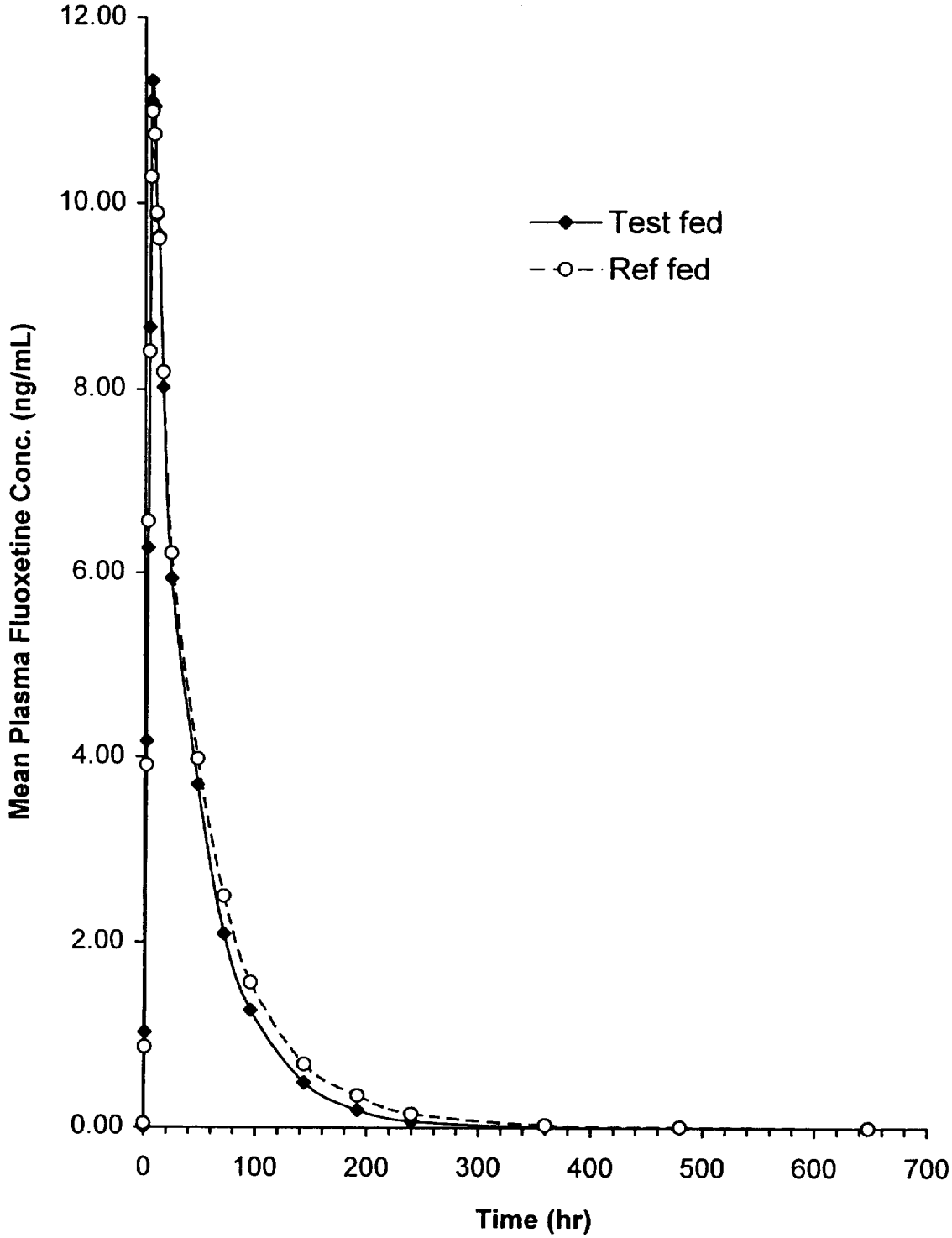

Figure 4. Mean Plasma Norfluoxetine Concentration-Time Plot: Fed Study, N=17