CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

BIOEQUIVALENCY REVIEW(S)

MAY 17 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-465 APPLICANT: Reddy-Cheminor, Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules
10 mg, 20 mg, 40 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. Your waiver request for fluoxetine hydrochloride 40 mg capsule is denied for the following reasons:

1. The Office of Generic Drugs generally does not grant upward waivers.
2. As confirmed by you, the innovator's 20 mg and 40 mg capsules are not proportionally formulated and do not have similar dissolution profiles.
3. Innovator's labeling states that fluoxetine's metabolism is not proportional to dose.
4. The Agency has no conclusive data to show proportional fluoxetine bioavailability between 20 mg and 40 mg capsules.

You are, therefore, requested to conduct a fasting study on your fluoxetine hydrochloride 40 mg capsules. However, you do not need to conduct a non-fasting study on the 40 mg capsules.

Sincerely yours,

/S/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 10 and 20 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:
>
> Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 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 reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, USP
10 mg, 20 mg, 40 mg
Study Amendment, 9/26/2000

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that dissolution testing as specified in USP 24, first supplement has been incorporated into your stability and quality control programs.

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 reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Fluoxetine Hydrochloride
10 mg, 20 mg and 40 mg Capsules
ANDA #75-465
Reviewer: Kuldeep R. Dhariwal
File name: 75465SDW.300

Reddy-Cheminor, Inc.
66 South Maple Avenue
Ridgewood, NJ 07450
Submission Date:
March 30, 2000

Review of an Amendment

September 24, 1998: Fasting and non-fasting studies on 20 mg capsules, dissolution data and waiver request for 10 mg strength.
December 10, 1998: Biostudies and dissolution data were acceptable. Waiver for 10 mg capsule granted.
September 20, 1999: Waiver request for an additional strength, 40 mg.
November 16, 1999: The following deficiencies were communicated to the firm: If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.
March 30, 2000: Response to November 16, 1999 deficiencies.

Firm's response:

1. **Capsule fill weight data:** The average fill weights were found to be 227 mg and 267 mg per capsule for 20 mg and 40 mg innovator products respectively. Thus, from the composition standpoint, 20 mg and 40 mg innovator capsules are not weight proportional. The fill weights for Cheminor products are 220 mg and 440 mg for 20 mg and 40 mg capsules respectively.

   Reviewer's comments: Firm's data confirm that the innovator strengths (20 mg and 40 mg) are not proportional. The test 20 mg and 40 mg capsules are weight proportional.

2. **IR spectrum:** IR spectra of 20 mg and 40 mg innovator capsules are similar indicating that the two strengths of innovator product contain same ingredients.

   Reviewer's comments: The infra-red spectra suggest only the qualitative similarity in chemical composition of the two strengths.

3. **Dissolution:** Cheminor conducted comparative dissolution studies on 2x20 mg, 1x40 mg Prozac® capsules and 1x40 mg Cheminor capsules. All three products dissolved greater than % in 20 minutes. The 40 mg innovator product and the 40 mg Cheminor product exhibit very similar dissolution profiles. The Prozac® 20 mg capsules show higher dissolution at 10 minutes time-point compared to both, Prozac® 40 mg and Cheminor 40 mg capsules. has calculated that following a 40 mg dose, the predicted Tmax is about 6.5 hours with a half-life of 38 hours. Hence, minor differences in dissolution profiles before the 20 minute time interval are unlikely to affect bioavailability.

   Reviewer's comments: The dissolution data given in Table 1 support the previous data. The F_2 comparison showed that dissolution profile of innovator 40 mg capsule is different from innovator 20 mg capsule (F_2=43.75) (review dated November 16, 1999; file name: 75465SDW.999).

4. **Biostudies:** Cheminor's fasting and food effect bioequivalence studies were conducted using 2x20 mg doses of the test and reference products. Therefore, a 40 mg dose of fluoxetine was tested *in vivo*. The products are immediate-release capsules and the only excipient for both the test and reference products is starch. The starch is used as a filler and the fact that the innovator 20 mg and 40 mg products are not weight proportional should not cause a difference *in vivo* between administration of a 2x20 mg dose or 1x40 mg dose.

   It should be noted that Cheminor conducted the biostudies for the 20 mg product prior to the approval and availability of the 40 mg innovator product. Cheminor's exhibit batch of the 40 mg capsules was manufactured and tested prior to the availability of the innovator 40 mg product.

   Reviewer's comments: A biostudy conducted using 2x20 mg capsule (40 mg dose) is not considered the same as a biostudy conducted using 1x40 mg capsule.

5. **Inference from reference listed drug:** The 40 mg product is listed in the Orange Book as the reference listed drug, the 10 mg and 20 mg products are not. This would indicate a level of similarity between the 10 mg, 20 mg, and 40 mg innovator products, such that biostudy waivers may be granted within the product line.

Reviewer's comments: The firm conducted biostudies on 20 mg strength and is requesting an upward waiver for 40 mg strength, which is usually not granted. The reservation in granting upward waiver in this case is due to the following reasons:

a) The reference 20 and 40 mg capsules are not proportionally formulated like the test 20 and 40 mg capsules.
b) The F_2 test between 20 and 40 mg reference capsules fails.
c) The labeling of the reference listed drug states that fluoxetine's metabolism is not proportional to dose.
d) The Agency has no conclusive data to show proportional fluoxetine bioavailability between 20 mg and 40 mg capsules.

6. **Chronology of events leading to Cheminor's biowaiver request:**
   - August 26, 1999: Innovator lists and advertises Prozac capsules, 40 mg on Lilly website.
   - September 3, 1999: Innovator launches Prozac capsules, 40 mg. The Orange Book cumulative supplement 7 (July 99) lists 20 mg Prozac capsule as RLD.
   - September 20, 1999: Cheminor amends ANDA 75-465 to request inclusion of 40 mg strength. At the time of this amendment, there is no RLD for Prozac 40 mg capsule.
   - October 18, 1999: The Orange Book cumulative supplement 8 (August 99) lists Prozac 40 mg capsule as RLD. This supplement, available to industry in October 1999, indicates the product was approved on June 15, 1999.

We acknowledge that the innovator 20 mg and 40 mg capsules are not weight proportional, however we believe that based on the data provided, a biowaiver for Cheminor's fluoxetine hydrochloride 40 mg capsule is supported. We respectfully request that the Agency reconsider the request for a waiver of *in vivo* bioavailability/bioequivalence study requirements for Cheminor's fluoxetine hydrochloride capsules, USP 40 mg.

Reviewer's comments:

1. The Cheminor's product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional. Therefore, the firm will be requested to conduct a fasting study on its fluoxetine hydrochloride 40 mg capsule.
2. The non-fasting study on 40 mg strength is not necessary. The firm has conducted a non-fasting study on 20 mg capsule (dose 2x20 mg) for the approval of 20 mg strength.

Recommendations:

The waiver of *in vivo* bioequivalence study requirements for fluoxetine hydrochloride 40 mg capsule manufactured by Cheminor is denied. The firm is requested to conduct a fasting study on 40 mg capsule. The non-fasting study on 40 mg capsule is not necessary.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 5/4/2000

Concur: /S/ Date 5/8/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride Capsules
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: March 30, 2000
File Name: 75465SDW.300

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes (USP 24)
Reference Drug: Prozac®
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Prozac capsule (Reference) Lot # 2 ND49M Strength(mg) 40			Prozac capsule (Reference) Lot # 1AD33A Strength(mg) 20 (2x20)		
	Mean %	Range	%CV	Mean %	Range	%CV
5	19		34.2	24		32.9
10	54		27.8	87		7.1
15	81		20.1	95		1.7
20	94		6.4	96		1.4
30	97		2.5	96		1.4
45	97		3.5	97		1.3

Sampling Times (Minutes)	Test Product Lot # E001 Strength(mg) 40			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
5	13		33.8			
10	58		20.9			
15	87		9.9			
20	95		2.3			
30	95		1.6			
45	96		1.5			

Fluoxetine Hydrochloride
10 mg and 20 mg Capsules
ANDA #75465
Reviewer: Kuldeep R. Dhariwal
Filename: 75465SDW.998

Cheminor Drugs Limited
7-1-27 Ameerpet
Hyderabad 500 016
India
Submission Date:
September 24, 1998

Review of Fasting and Non-fasting Bioequivalence Studies, Dissolution Data and Waiver Request

The firm has submitted single dose bioequivalence studies under fasting and non-fasting conditions and dissolution data comparing its fluoxetine hydrochloride 20 mg capsules with Dista Pharmaceutical's (Lilly) Prozac® 20 mg capsules. The firm has also requested for waiver of *in vivo* bioequivalence study requirements for its 10 mg capsules. To support the request, the firm has submitted comparative dissolution profiles on 10 mg capsules of its product and reference listed drug Prozac®.

Introduction:

Fluoxetine hydrochloride is an antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemic mixture (50/50) of R and S enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity.

Following a single oral dose of 40 mg, peak plasma concentrations (15-55 ng/mL) are observed between 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be taken with or without food. It is extensively metabolized in liver to norfluoxetine and a number of unidentified metabolites. The only identified active metabolite, norfluoxetine is formed by demethylation of fluoxetine. The elimination half life of fluoxetine is about 1 to 3 days and that of norfluoxetine is 4 to 16 days.

Fluoxetine is indicated for the treatment of depression. The initial recommended dose is 20 mg/day administered in the morning. Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (i.e. morning and noon) and should not exceed a maximum dose of 80 mg/day.

The reference listed drug is Prozac® (Dista Pharmaceuticals-Lilly) and is available as 10 and 20 mg capsules (pulvules) and as 20 mg/5 mL liquid oral solution.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol #: 971712
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site:
Analytical Site:
Principal Investigator:
Study Dates: Period I November 8, 1997
Period II January 31, 1998
Analysis Dates: March 2 to April 8, 1998
Study Design: Randomized, two-way crossover design with a wash-out period of 12 weeks
Randomization Scheme: AB: 2,4,7,8,9,11,13,14,15,17,19,21,25, 26,28,32,34,36
BA: 1,3,5,6,10,12,16,18,20,22,23,24, 27,29,30,31,33,35

Treatments:

A= Fluoxetine Hydrochloride, 2x20 mg capsules; Cheminor Drugs; Batch #001; Batch size: capsules; Manufacture Date: September 1, 1997; Assay: %; Uniformity of dosage units: %

B= Prozac®, 2x20 mg capsules; Dista Pharmaceuticals; Batch #1AD33A; Expiry Date: March 2000; Assay: %; Uniformity of dosage units: %

Formulation of Test Product: Table 1
Subjects: 36 male subjects were enrolled according to the criteria specified in the protocol

Housing:	From the evening before dosing until after the 36 hour blood draw
Dosing:	After 10 hour fast, with 240 ml water
Sample Collection:	Blood samples (10 mL) were collected at predose (0 h) and at following times after dosing:1,2,3,4,5,6,7,8,10,12,16, 24,36,48,60,72,84,96,120,144,168,336, 504 and 672 hours.

B. Study Results:

1. Clinical:

Drop-outs:	Subject #23 and 33 withdrew after period I. Subject #28 elected to withdraw after 36 hour blood draw in period II for medical reasons. Subject #28 vomited three times after dosing in period II (reference drug) and was later diagnosed with Crohn's disease. Thus, 33 subjects completed the study. Samples from first 30 subjects were analyzed.
Adverse Events:	Some subjects experienced nausea, headache, lightheaded etc. The events were comparable on test and reference drugs. Subject #30 had loose stools after 2 h of dosing in period II (test drug) and subject #28 had vomiting (see above).
Protocol Deviations:	There were a few sampling time deviations. The pharmacokinetic parameters were calculated using actual sampling times.

2. Analytical:

Method:	
Internal Standard:	
Linearity:	

Regression:

Accuracy:

Precision:

Reassays:

The firm has provided following pre-study method validation results:

Linearity:

Accuracy:

Precision:

Recovery:

Stability:

3. Pharmacokinetics/Statistics:

FLUOXETINE:		
Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	97.02-103.53%
	$LAUC_{0-inf}$	97.56-103.83%
	LC_{max}	99.62-106.00%
Test/Reference Ratio:	AUC_{0-t}	1.01 (0.82-1.19)
	AUC_{0-inf}	1.01 (0.83-1.19)
	C_{max}	1.03 (0.82-1.26)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.95 (0.89-0.98)
	Reference	0.96 (0.92-0.98)
NORFLUOXETINE:		
Mean Plasma Concentrations:	Table 3 and Figure 2	
Pharmacokinetic Parameters:	Table 3	

90% Confidence Intervals:	$LAUC_{0-t}$	100.76-106.35%
	$LAUC_{0-inf}$	101.25-105.92%
	LC_{max}	99.87-109.19%
Test/Reference Ratio:	AUC_{0-t}	1.04 (0.86-1.36)
	AUC_{0-inf}	1.04 (0.92-1.27)
	C_{max}	1.06 (0.82-1.90)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.95 (0.79-0.99)
	Reference	0.95 (0.77-0.98)

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.
2. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
3. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits.
   Fluoxetine: There was no statistically significant period, sequence or treatment effect for any of these parameters.
   Norfluoxetine: There was significant period and treatment effect for $LAUC_{0-t}$ and $LAUC_{0-inf}$. In addition, significant sequence effect was observed for LC_{max}. The significant sequence effect is acceptable because it is a single dose study including healthy subjects and is based on an acceptable study protocol, contains an acceptable validated assay methodology and the study data are acceptable.
4. The fasting study is acceptable.

Bioavailability of Fluoxetine HCl Capsules, 20 mg Under Non-Fasting Conditions:

A. Study Information:

Protocol #:	971713
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	
Study Dates:	Period I November 1, 1997
	Period II January 24, 1998
	Period III April 18, 1998
Analysis Dates:	May 19 to June 4, 1998

Study Design: Randomized, three-way crossover design with a wash-out period of 12 weeks

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

Treatments:

A= Fluoxetine Hydrochloride, 2x20 mg capsules; Cheminor Drugs; Batch #001; administered after a 10 hour fast

B= Fluoxetine Hydrochloride, 2x20 mg capsules; Cheminor Drugs; Batch #001; administered after a standard breakfast

C= Prozac®, 2x20 mg capsules; Dista Pharmaceuticals; Batch #1AD33A; administered after a standard breakfast

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

Subjects: 22 male subjects were enrolled according to inclusion/exclusion criteria specified in the protocol

Dosing: Treatments B and C: Subjects were given OGD approved standardized breakfast 30 minutes before dosing after a fast lasting at least 9.5 hours. The dose was given with 240 mL of water. Treatment A: Subjects were given a single oral dose of the assigned formulation with 240 mL of water after a 10 hour fast.

Sample Collection: Blood samples were collected at predose (0 h) and at following times after dosing: 1,2.5,4,5,6,7,8,9,11,16,24, 36,48,60,72,84,96,120,144,168,336,504 and 672 hours.

Housing: From the evening before dosing until after the 36 hour blood draw

B. Study Results:

1. Clinical:

Drop-outs: Subject #11 and 18 withdrew after period I and II respectively. Thus, 20 subjects completed the study. Samples from first 18 subjects were analyzed.

Adverse Events: Some subjects experienced headache, sore throat, coughing etc. The events were comparable on test and reference drugs.

Protocol Deviations: There were a few sampling time deviations. The pharmacokinetic parameters were calculated using actual sampling times.

2. Analytical:

Method:
Internal Standard:
Accuracy:

Precision:

Reassays:

3. Pharmacokinetics/Statistics:

FLUOXETINE:
Mean Plasma Concentrations: Table 4, Figure 3
Pharmacokinetic Parameters: Table 5

AUC_{0-t}/AUC_{0-inf} Ratios:	Test Fasting	0.95	(0.87-0.98)
	Test Non-fasting	0.96	(0.92-0.98)
	Ref. Non-fasting	0.95	(0.88-0.98)
Test non-fasting/Ref. non-fasting:	AUC_{0-t}	1.08	(0.83-1.34)
	AUC_{0-inf}	1.06	(0.85-1.28)
	C_{max}	1.07	(0.86-1.36)

NORFLUOXETINE:

Mean Plasma Concentrations:	Table 6, Figure 4		
Pharmacokinetic Parameters:	Table 7		
AUC_{0-t}/AUC_{0-inf} Ratios:	Test Fasting	0.94	(0.77-0.99)
	Test Non-fasting	0.93	(0.74-0.98)
	Ref. Non-fasting	0.94	(0.78-0.98)
Test non-fasting/Ref. non-fasting:	AUC_{0-t}	1.04	(0.86-1.26)
	AUC_{0-inf}	1.06	(0.84-1.32)
	C_{max}	1.06	(0.81-1.95)

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.
2. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
3. Ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test non-fasting and reference non-fasting are within acceptable limits. The non-fasting study is acceptable.

In Vitro Dissolution Testing:

The dissolution testing was done using FDA method: 900 mL water, apparatus II (paddles) at 50 rpm. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence study. The test and reference products dissolve more than % in 30 minutes (Table 8).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 10 mg capsules. The comparative quantitative compositions of 10 and 20 mg capsules are shown in Table 1. The 10 mg capsules are proportionally similar in their active and inactive ingredients to 20 mg capsules. The amount of pregelatinized starch is adjusted to account for the difference in the amount of active ingredient between the two strengths.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Cheminor Drugs on its fluoxetine hydrochloride

capsules, 20 mg, lot #001, comparing it to the reference product Prozac® capsules 20 mg, lot #1AD33A manufactured by Dista (Lilly) has been found acceptable by the Division of Bioequivalence. The study demonstrates that Cheminor's fluoxetine hydrochloride 20 mg capsule is bioequivalent to the reference product, Prozac® 20 mg capsule manufactured by Dista (Lilly).

2. The bioequivalence study conducted under fed conditions by Cheminor Drugs on its fluoxetine hydrochloride capsules 20 mg, lot #001, comparing it to the reference product Prozac® capsules 20 mg, lot #1AD33A manufactured by Dista (Lilly) has been found acceptable by the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Cheminor's fluoxetine hydrochloride 20 mg capsules is similar to that of the reference product Prozac® 20 mg capsule manufactured by Dista (Lilly).

3. The dissolution testing conducted by Cheminor on its fluoxetine hydrochloride 10 mg and 20 mg capsules is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study comparing its 20 mg capsule of the test product with 20 mg capsule of the reference product Prozac® manufactured by Dista. The formulation for the 10 mg strength of the test product is proportionally similar to the 20 mg strength of the test product which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 10 mg capsules of the test product is granted. The 10 mg capsule of the test product is therefore deemed bioequivalent to the 10 mg capsule of Prozac® manufactured by Dista (Lilly).

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL water at 37°C using apparatus II (paddles) at 50 rpm. The test products should meet the following specifications:

> Not less than % of the labeled amount of fluoxetine in the dosage form is dissolved in 30 minutes.

5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

/S/ Date 12/8/1998

Concur: /S/ Date 12/10/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Table 1

Comparative Quantitative Composition of Fluoxetine Capsules

Ingredients	Strength			
	10 mg		20 mg	
	mg/capsule	%	mg/capsule	%
Fluoxetine Hydrochloride	11.18*	5.00	22.36**	10.00
Pregelatinized starch				
Total				

* equivalent to 10 mg fluoxetine
** equivalent to 20 mg fluoxetine

Hard Gelatin Capsule Components:
Empty gelatin capsule contains: FD&C Blue #1, titanium dioxide, gelatin, silicon dioxide, sodium lauryl sulfate

Table 2

MEAN PLASMA FLUOXETINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.25	1.07	1.21	1.04	1.03
2	7.55	3.63	7.01	3.85	1.08
3	13.98	4.62	12.95	5.38	1.08
4	20.09	5.57	17.25	4.57	1.16
5	22.60	5.25	21.42	4.92	1.05
6	24.37	5.45	24.25	5.92	1.00
7	23.43	5.04	23.25	6.12	1.01
8	23.62	5.50	22.84	5.44	1.03
10	21.45	5.15	21.17	4.99	1.01
12	20.45	4.72	20.24	5.00	1.01
16	18.03	4.45	17.62	4.95	1.02
24	14.45	4.38	14.72	4.47	0.98
36	11.06	4.14	11.21	4.17	0.99
48	8.52	3.61	9.19	4.10	0.93
60	6.71	3.56	6.67	3.52	1.01
72	5.75	3.43	5.59	3.29	1.03
84	4.46	3.12	4.50	3.19	0.99
96	3.73	2.76	3.80	3.12	0.98
120	2.50	2.53	2.44	2.39	1.03
144	1.68	2.10	1.66	2.23	1.02
168	1.16	1.76	1.12	1.88	1.03
336	0.16	0.51	0.17	0.56	0.97
504	0.02	0.12	0.02	0.11	1.06
672	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1251.30	719.48	1246.10	736.55	1.00
AUCT	1193.07	689.98	1194.07	714.48	1.00
CMAX	25.42	5.40	24.86	6.04	1.02
KE	0.02	0.01	0.02	0.01	0.96
LAUCI	1114.60	0.46	1107.48	0.46	1.01
LAUCT	1062.88	0.46	1060.55	0.46	1.00
LCMAX	24.82	0.23	24.15	0.25	1.03
THALF	39.91	18.06	37.80	16.62	1.06
TMAX	6.44	1.48	6.40	0.81	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1251.30	1246.10	1.00	97.20	103.64
AUCT	1193.07	1194.07	1.00	96.59	103.24
CMAX	25.42	24.86	1.02	98.86	105.64
LAUCI	1114.60	1107.48	1.01	97.56	103.83
LAUCT	1062.88	1060.55	1.00	97.02	103.53
LCMAX	24.82	24.15	1.03	99.62	106.00

Table 3

MEAN PLASMA NORFLUOXETINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.07	0.21	0.05	0.21	1.23
2	1.62	0.91	1.53	0.91	1.06
3	3.42	1.50	3.14	1.80	1.09
4	5.60	2.35	4.63	1.81	1.21
5	7.13	2.66	6.29	2.29	1.13
6	8.80	3.12	8.01	2.63	1.10
7	9.13	3.08	8.56	2.83	1.07
8	9.75	3.23	9.05	3.11	1.08
10	10.78	3.26	10.12	3.61	1.07
12	11.55	4.03	10.86	3.54	1.06
16	12.57	4.61	11.58	3.66	1.09
24	12.39	4.21	11.91	3.66	1.04
36	15.66	4.83	15.39	4.60	1.02
48	15.53	5.04	15.76	4.84	0.99
60	16.44	4.74	16.16	4.83	1.02
72	15.98	5.01	15.08	4.61	1.06
84	16.05	4.79	15.89	4.79	1.01
96	15.12	4.41	15.06	4.38	1.00
120	13.91	4.11	13.80	4.36	1.01
144	13.19	3.90	12.13	3.48	1.09
168	11.73	3.56	11.25	3.87	1.04
336	5.26	2.46	5.08	2.70	1.04
504	2.15	1.92	2.14	1.87	1.00
672	0.70	1.13	0.74	1.09	0.95

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4846.80	1865.68	4726.53	1937.94	1.03
AUCT	4571.43	1608.47	4443.20	1681.59	1.03
CMAX	18.15	5.34	17.35	4.90	1.05
KE	0.01	0.00	0.01	0.00	1.00
LAUCI	4545.02	0.37	4388.91	0.39	1.04
LAUCT	4296.59	0.37	4150.51	0.38	1.04
LCMAX	17.33	0.32	16.60	0.32	1.04
THALF	128.75	42.73	129.86	47.38	0.99
TMAX	66.81	21.06	65.21	20.83	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	4846.80	4726.53	1.03	100.36	104.73
AUCT	4571.43	4443.20	1.03	100.47	105.30
CMAX	18.15	17.35	1.05	99.54	109.66
LAUCI	4545.02	4388.91	1.04	101.25	105.92
LAUCT	4296.59	4150.51	1.04	100.76	106.35
LCMAX	17.33	16.60	1.04	99.87	109.19

Table 4

MEAN PLASMA FLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, n=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	0.97	0.84	1.18	2.08	1.65	2.43	0.82
2.5	9.40	3.98	10.14	8.92	9.33	8.01	0.93
4	16.56	6.22	16.26	5.64	14.27	7.00	1.02
5	19.31	4.87	18.78	4.26	17.76	7.27	1.03
6	21.51	4.69	22.56	5.80	21.73	5.50	0.95
7	21.45	4.42	23.32	4.87	21.93	5.71	0.92
8	20.06	3.91	22.10	4.53	20.79	5.31	0.91
9	19.27	3.14	21.36	4.68	19.92	5.72	0.90
11	18.05	3.87	19.88	3.83	18.78	4.55	0.91
16	15.79	3.50	16.82	4.33	16.54	4.74	0.94
24	12.99	3.58	12.90	3.83	13.14	3.84	1.01
36	10.13	3.60	11.35	4.20	10.83	3.98	0.89
48	8.04	3.44	8.35	3.92	7.60	3.37	0.96
60	6.21	3.54	6.87	4.02	6.36	3.28	0.90
72	5.08	3.37	5.28	3.51	5.26	3.32	0.96
84	4.15	3.04	4.52	2.97	4.06	2.64	0.92
96	3.42	2.73	3.72	3.18	3.50	2.92	0.92
120	2.33	2.43	2.74	2.95	2.39	2.37	0.85
144	1.67	2.22	1.88	2.41	1.82	2.40	0.89
168	1.23	2.08	1.39	2.36	1.27	2.18	0.89
336	0.33	1.01	0.40	1.10	0.33	1.03	0.83
504	0.08	0.33	0.15	0.50	0.11	0.48	0.51
672	0.05	0.20	0.05	0.21	0.06	0.25	0.92

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN PLASMA FLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
1	0.58	0.71
2.5	1.01	1.09
4	1.16	1.14
5	1.09	1.06
6	0.99	1.04
7	0.98	1.06
8	0.96	1.06
9	0.97	1.07
11	0.96	1.06
16	0.95	1.02
24	0.99	0.98
36	0.94	1.05
48	1.06	1.10
60	0.98	1.08
72	0.97	1.00
84	1.02	1.11
96	0.98	1.07
120	0.97	1.15
144	0.92	1.03
168	0.97	1.09
336	0.99	1.20
504	0.68	1.33
672	0.78	0.85

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 5

FLUOXETINE ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	1211.11	871.31	1315.00	971.94	1243.11	916.07	0.92
AUCT	1140.11	805.28	1258.44	930.88	1166.33	840.70	0.91
CMAX	22.40	4.32	24.31	4.93	23.17	5.47	0.92
KE	0.02	0.01	0.02	0.01	0.02	0.01	1.10
LAUCI	1031.98	0.53	1103.02	0.56	1045.13	0.56	0.94
LAUCT	978.74	0.52	1054.95	0.57	987.42	0.55	0.93
LCMAX	21.99	0.20	23.84	0.20	22.51	0.25	0.92
THALF	45.48	35.05	46.96	33.02	47.01	36.72	0.97
TMAX	6.45	1.10	6.47	1.38	6.61	1.58	1.00

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.97	1.06
AUCT	0.98	1.08
CMAX	0.97	1.05
KE	1.09	0.99
LAUCI	0.99	1.06
LAUCT	0.99	1.07
LCMAX	0.98	1.06
THALF	0.97	1.00
TMAX	0.98	0.98

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	1176.28	1273.66	1205.03	0.92	0.98	1.06
AUCT	1109.09	1219.94	1131.57	0.91	0.98	1.08
CMAX	22.13	23.98	22.87	0.92	0.97	1.05
LAUCI	994.18	1057.08	1004.22	0.94	0.99	1.05
LAUCT	944.43	1011.93	949.98	0.93	0.99	1.07
LCMAX	21.73	23.53	22.24	0.92	0.98	1.06

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 6

MEAN PLASMA NORFLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, n=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	0.03	0.13	0.03	0.13	0.12	0.27	1.02
2.5	2.23	1.12	2.27	2.12	2.17	2.33	0.98
4	4.96	2.18	4.72	2.46	4.31	2.84	1.05
5	6.88	3.10	6.00	2.87	6.02	3.85	1.15
6	8.75	3.78	8.15	3.96	7.95	3.92	1.07
7	9.42	3.86	9.08	4.16	8.89	4.47	1.04
8	9.78	3.85	9.88	4.63	8.73	4.09	0.99
9	10.31	4.58	10.39	4.92	9.04	4.29	0.99
11	11.18	4.71	10.76	4.77	10.10	4.44	1.04
16	12.90	5.64	12.35	5.15	12.17	5.16	1.04
24	12.88	5.06	11.71	4.52	12.18	4.93	1.10
36	15.86	6.18	16.44	6.21	16.12	6.82	0.96
48	15.21	5.16	14.99	4.94	14.75	5.30	1.01
60	16.46	5.98	17.14	6.23	16.54	6.42	0.96
72	15.57	5.46	14.78	5.09	14.84	4.71	1.05
84	16.42	5.78	16.72	5.78	15.57	5.13	0.98
96	14.51	5.01	14.90	4.67	14.57	4.33	0.97
120	14.24	5.06	14.36	4.49	13.80	4.76	0.99
144	13.32	4.54	13.43	3.90	12.73	3.98	0.99
168	12.51	4.56	11.83	3.51	10.91	3.29	1.06
336	5.48	2.65	5.43	2.87	5.16	2.26	1.01
504	2.03	1.74	2.12	2.05	1.98	1.46	0.96
672	0.80	1.27	0.79	1.50	0.74	1.07	1.02

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN PLASMA NORFLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
1	0.27	0.27
2.5	1.03	1.05
4	1.15	1.10
5	1.14	1.00
6	1.10	1.02
7	1.06	1.02
8	1.12	1.13
9	1.14	1.15
11	1.11	1.07
16	1.06	1.01
24	1.06	0.96
36	0.98	1.02
48	1.03	1.02
60	1.00	1.04
72	1.05	1.00
84	1.05	1.07
96	1.00	1.02
120	1.03	1.04
144	1.05	1.05
168	1.15	1.08
336	1.06	1.05
504	1.03	1.07
672	1.08	1.06

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 7

NORFLUOXETINE ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	4983.50	1952.62	4974.39	1800.80	4708.83	1456.80	1.00
AUCT	4665.17	1688.98	4582.17	1434.64	4405.28	1317.09	1.02
CMAX	18.13	6.10	19.21	6.63	18.31	6.18	0.94
KE	0.01	0.00	0.01	0.00	0.01	0.00	1.03
LAUCI	4608.22	0.42	4694.30	0.35	4473.83	0.34	0.98
LAUCT	4330.69	0.42	4351.63	0.34	4185.60	0.35	1.00
LCMAX	16.92	0.41	17.83	0.43	17.11	0.41	0.95
THALF	130.49	53.57	136.10	57.24	132.06	51.61	0.96
TMAX	64.26	28.38	66.59	25.38	67.34	29.43	0.97

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.06	1.06
AUCT	1.06	1.04
CMAX	0.99	1.05
KE	1.02	0.98
LAUCI	1.03	1.05
LAUCT	1.03	1.04
LCMAX	0.99	1.04
THALF	0.99	1.03
TMAX	0.95	0.99

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	4933.20	4917.74	4655.36	1.00	1.06	1.06
AUCT	4641.92	4553.55	4379.35	1.02	1.06	1.04
CMAX	18.38	19.38	18.52	0.95	0.99	1.05
LAUCI	4578.25	4657.66	4441.82	0.98	1.03	1.05
LAUCT	4316.41	4331.24	4168.89	1.00	1.04	1.04
LCMAX	17.16	18.01	17.32	0.95	0.99	1.04

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg and 20 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 24, 1998
File Name: 75465SDW.998

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac® (Dista)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 001A Strength(mg) 10			Reference Product Lot # OARO4A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75.0		16.9	90.5		4.2
20	98.8		3.5	93.6		2.7
30	98.9		2.1	97.5		5.0
45	99.2		3.9	96.3		3.6

Sampling Times (Minutes)	Test Product Lot # 001 Strength(mg) 20			Reference Product Lot # 1AD33A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	69.3		13.6	80.4		6.6
20	97.2		2.4	93.3		3.3
30	97.8		1.3	94.4		2.6
45	99.0		1.4	95.2		2.7

BIOEQUIVALENCY-COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 10 and 20 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 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 reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

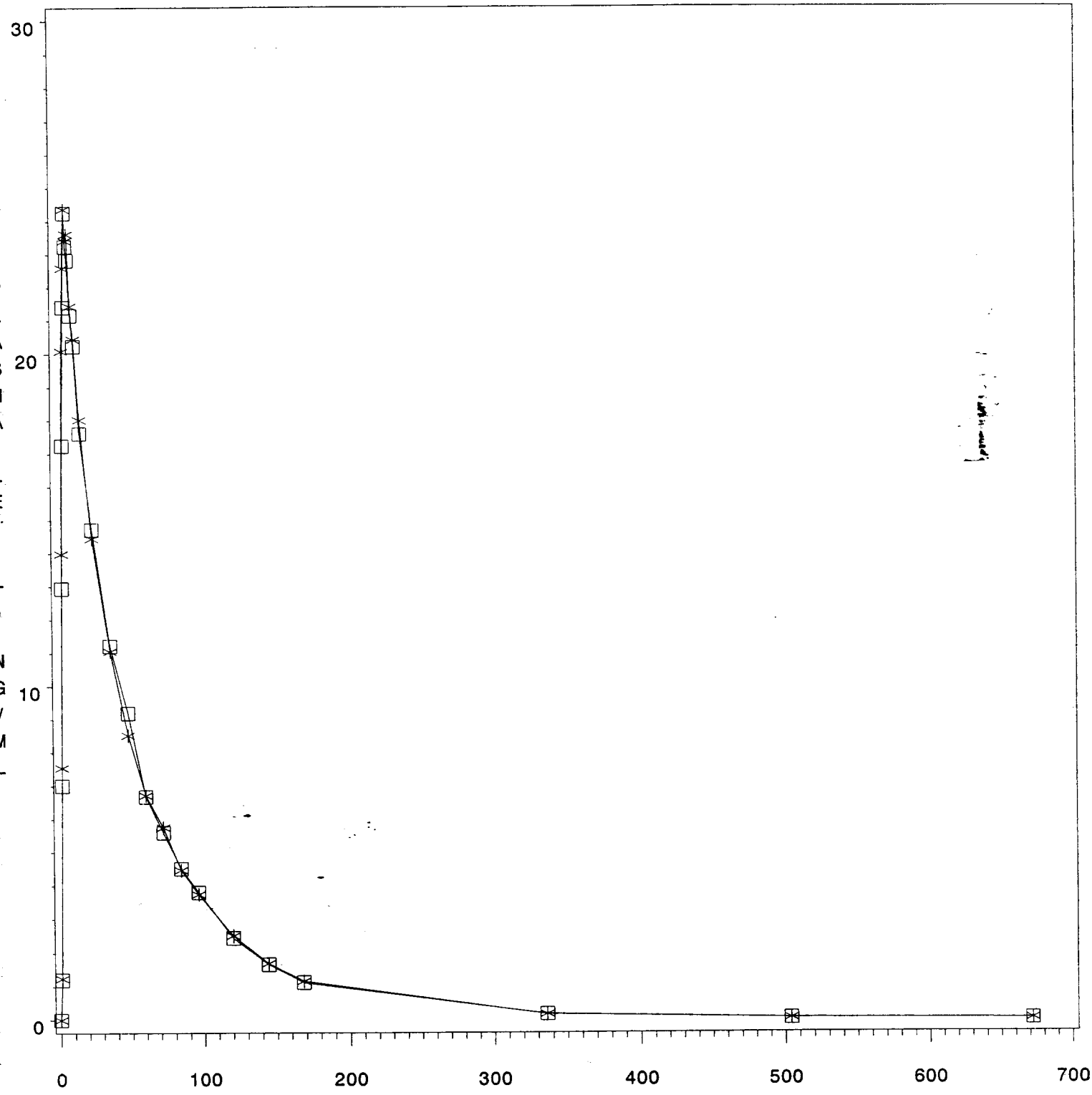
Sincerely yours,

/S/

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

FIG 1. PLASMA FLUOXETINE LEVELS

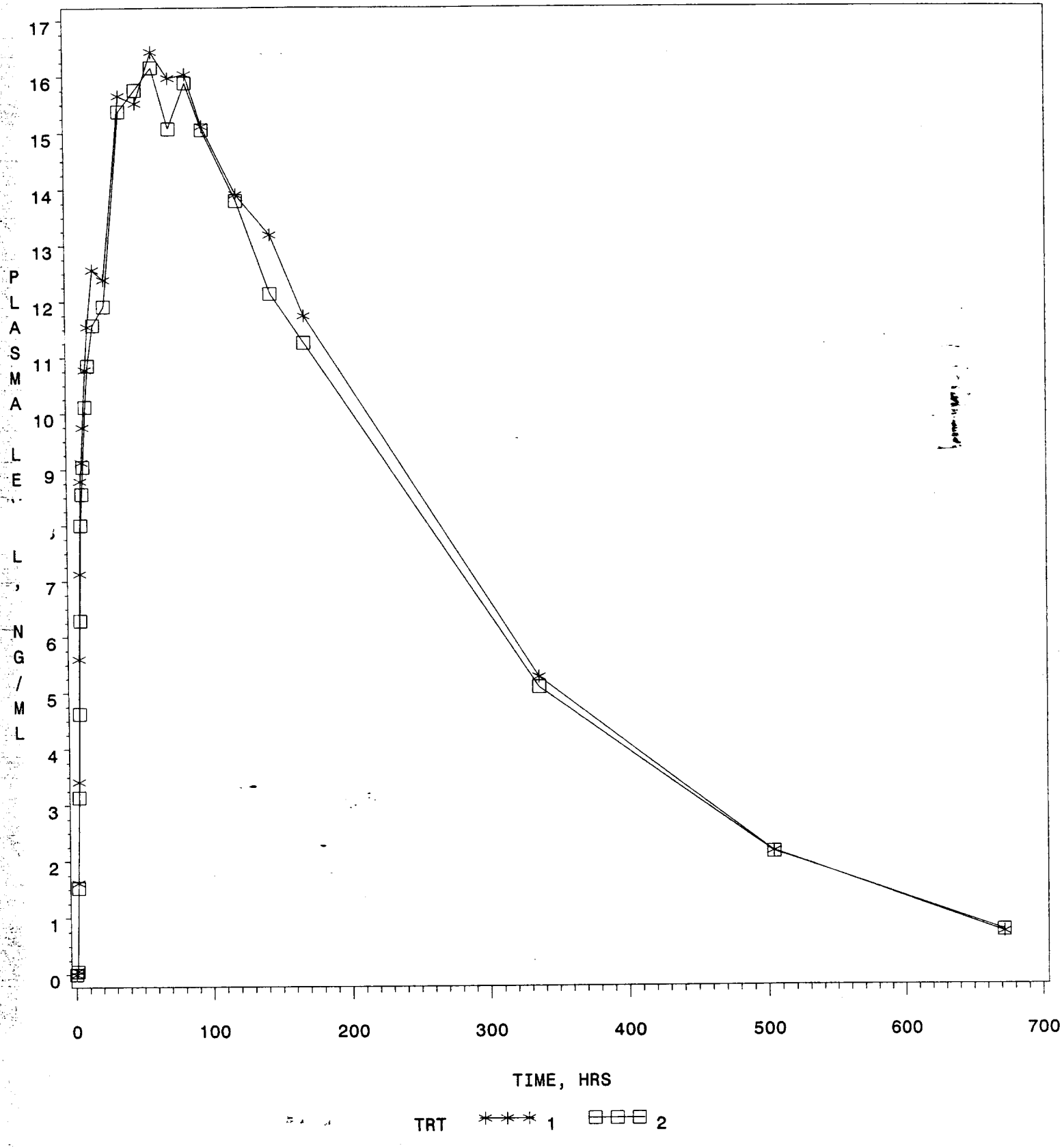
FLUOXETINE HCl CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=2 X 20 MG



1=TEST(CHEMINOR) 2=REF(DISTA)

FIG 2. PLASMA NORFLUOXETINE LEVELS

FLUOXETINE HCl CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=2 X 20 MG



1=TEST(CHEMINOR) 2=REF(DISTA)

FIG 3. PLASMA FLUOXETINE LEVELS

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING/NONFASTING CONDITIONS
DOSE=2 X 20 MG

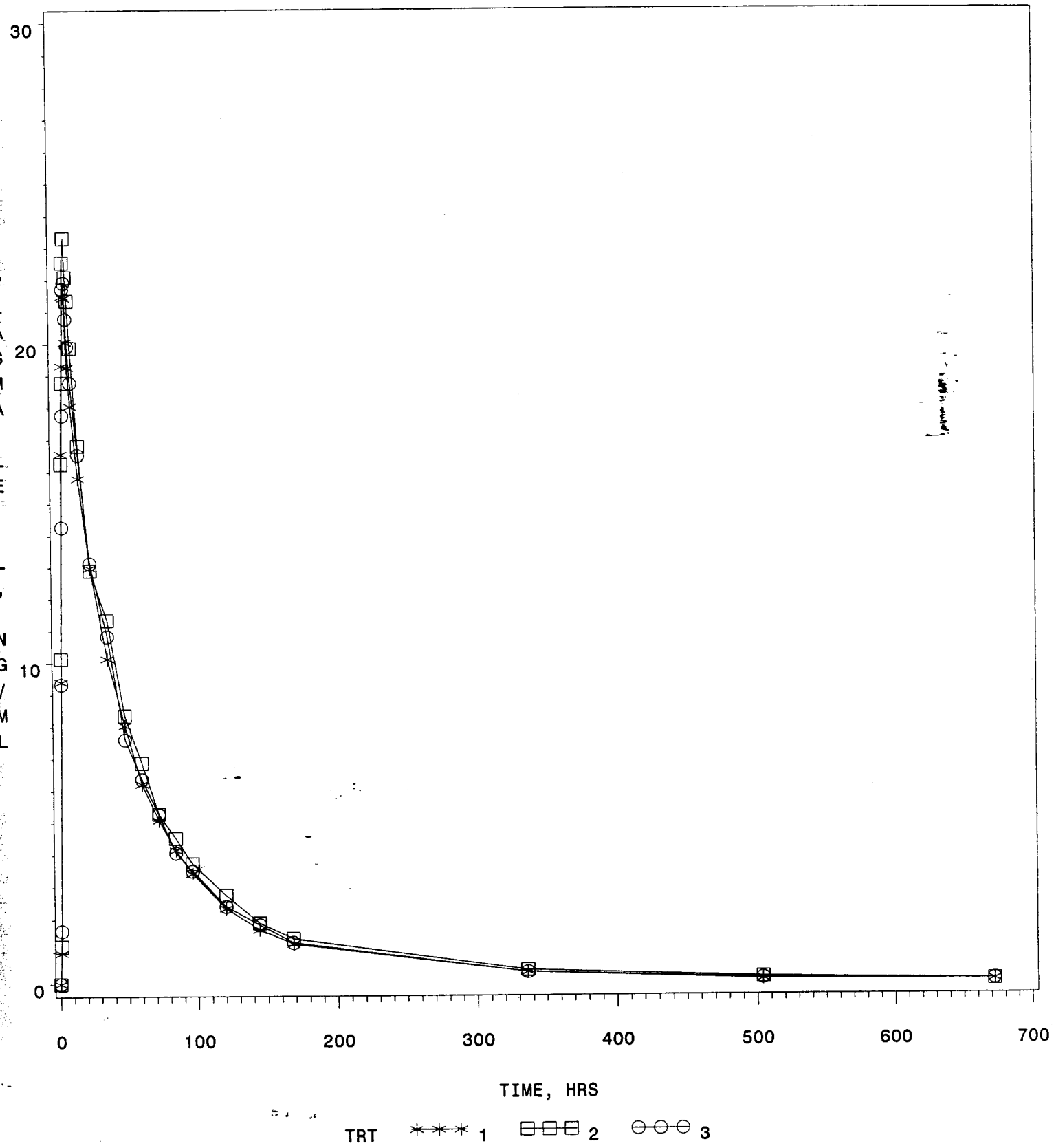
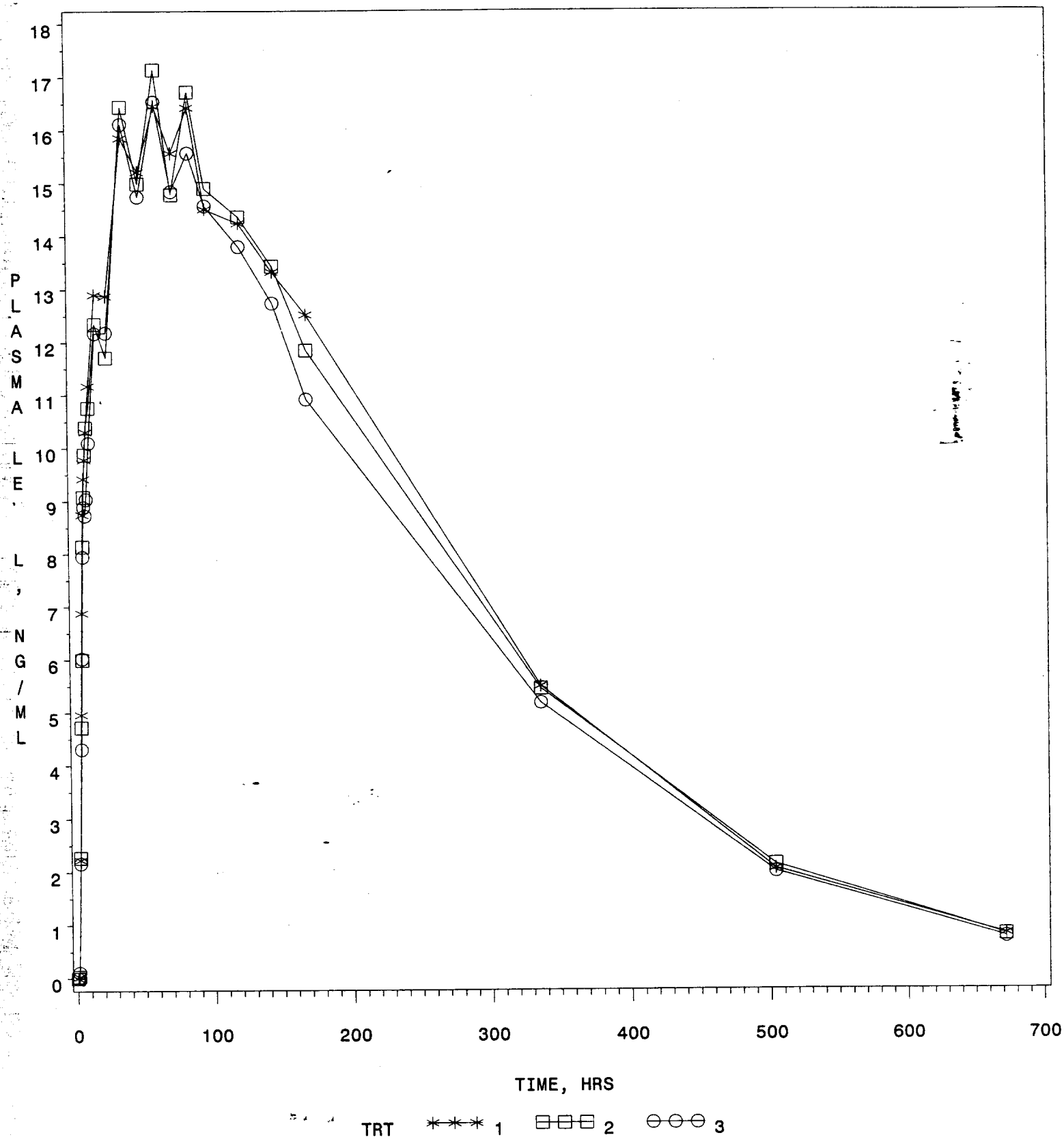


FIG 4. PLASMA NORFLUOXETINE LEVELS

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING/NONFASTING CONDITIONS
DOSE=2 X 20 MG



1=TEST(FAST) 2=TEST(FED) 3=REF(FED)

3.1

NOV 24 1999

DAVU

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsule
10 mg, 20 mg, 40 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.

Sincerely yours,

/S/

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

Fluoxetine Hydrochloride
10 mg, 20 mg and 40 mg Capsules
ANDA #75-465
Reviewer: Kuldeep R. Dhariwal
File name: 75465SDW.999

Cheminor Drugs Limited
7-1-27 Ameerpet
Hyderabad 500 016
India
Submission Date:
September 20, 1999

Review of an amendment to include Fluoxetine Capsules, 40 mg as additional dosage strength

September 24, 1998: Fasting and Non-fasting studies on 20 mg capsules, dissolution data and waiver request for 10 mg strength.
December 10, 1998: Biostudies and dissolution data were acceptable. Waiver for 10 mg capsules granted.
September 20, 1999: This submission containing waiver request for an additional strength, 40 mg.

Reference Listed Drug: Prozac® by Lilly (Dista).
Available as:
Capsules 10 mg, 20 mg, and 40 mg
Tablet 10 mg
Oral solution 20 mg/5 mL

Comments:

1. The comparative formulation of the test 10 mg, 20 mg, and 40 mg capsules is given in Table 1. The formulation of the reference drug is given in Table 2.
2. The dissolution profile of all three strengths is given in Table 3. All three strengths meet specification of NLT % (Q) in 30 minutes. The bio-study was done on 20 mg strength and therefore 10 and 40 mg strengths are compared with this strength for F_2 comparisons:

Test 20 mg vs. Test 10 mg	74.92
Test 20 mg vs. Test 40 mg	60.41
Ref 20 mg vs. Ref 10 mg	63.35
Ref 20 mg vs. Ref 40 mg	**43.75**
Test 20 mg vs. Ref 20 mg	59.39
Test 10 mg vs. Ref 10 mg	53.82
Test 40 mg vs. Ref 40 mg	79.68

3. **NOT TO BE RELEASED UNDER FOI**

The innovator, Lilly (Dista) requested for biowaiver for approval of Prozac® 40 mg capsule in June 1998. The Agency denied the waiver based on failed dissolution profile comparison, nonlinear kinetics and compositional disproportionality between the proposed strength and the approved strengths (10 and 20 mg). The 40 mg strength was approved in June 1999 based on biostudy.

The 10 and 20 mg test capsules have identical total weights. The proposed 40 mg capsule is proportionally formulated to 20 mg capsule. The 10 and 40 mg capsules pass F_2 test when compared with 20 mg capsule. However, the reference 20 and 40 mg capsules are not proportionally formulated and the reference 40 mg capsule fails F_2 test when compared with reference 20 mg capsule.

Cheminor's 10 and 20 mg fluoxetine hydrochloride capsules are not yet approved. The status of this ANDA is 'pending review'.

The waiver of *in vivo* biostudy for test 40 mg capsule will be denied for following reasons:

a. The reference 20 and 40 mg capsules are not proportionally formulated like the test 20 and 40 mg capsules.
b. The F_2 test between 20 and 40 mg reference capsules fails.
c. The approval of reference 40 mg capsule was based on biostudy.

4. The firm may conduct a fasting study on 40 mg strength. The non-fasting study on this strength is not necessary. The firm has conducted a non-fasting study on 20 mg capsule (dose 2x20 mg) for the approval of 20 mg strength.

Recommendations:

The waiver of *in vivo* bioequivalence study requirements for fluoxetine hydrochloride 40 mg capsule manufactured by Cheminor Drugs is denied. The firm may conduct a fasting study on 40 mg strength.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 10/22/1999

Concur: /S/ Date 11/16/99

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

NOT TO BE RELEASED UNDER FOI

Table 1

Comparative Formulation of Fluoxetine Capsules (Test Drug)

Ingredient	Strength					
	10 mg		20 mg		40 mg	
	mg	%	mg	%	mg	%
Fluoxetine Hydrochloride	11.18*	5.08	22.36**	10.16	44.72***	10.16
Pregelatinized starch						
Total Fill Weight						

*equivalent to 10 mg fluoxetine, ** equivalent to 20 mg fluoxetine, *** equivalent to 40 mg fluoxetine

Hard gelatin capsule components: FD&C Blue #1, titanium dioxide, gelatin, silicon dioxide, sodium lauryl sulfate

10 mg: opaque light blue capsule imprinted "FLUOXETINE 10 mg" and "SHN"

20 mg: opaque light blue and light turquoise blue imprinted "FLUOXETINE 20 mg" and "SHN"

40 mg: opaque light blue and opaque white imprinted "FLUOXETINE" 40 mg" and "SHN"

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Table 2

Comparative Quantitative Composition of Prozac Capsules (Reference Drug)#

Ingredient	Strength					
	10 mg		20 mg		40 mg	
	mg	%	mg	%	mg	%
Fluoxetine Hydrochloride	11.18*	4.86	22.36**	9.72	44.71***	16.75
Pregelatinized starch						
Total Fill Weight						

taken from bio-pharm review dated 11/23/98

*equivalent to 10 mg fluoxetine, ** equivalent to 20 mg fluoxetine, *** equivalent to 40 mg fluoxetine

10 mg: opaque green and green, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body

20 mg: opaque green cap and off-white body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body

40 mg: opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 20, 1999
File Name: 75465SDW.999

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac® (Dista)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 001A Strength(mg) 10			Reference Product Lot # OARO4A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75.0		16.9	90.5		4.2
20	98.8		3.5	93.6		2.7
30	98.8		2.1	97.5		5.0
45	99.2		3.9	96.3		3.6

Sampling Times (Minutes)	Test Product Lot # 001 Strength(mg) 20			Reference Product Lot # 1AD33A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	69.3		13.6	80.4		6.6
20	97.2		2.4	93.3		3.3
30	97.8		1.3	94.4		2.6
45	99.0		1.4	95.2		2.7

Table 3 Continued... In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 20, 1999 .
File Name: 75465SDW.999

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac® (Dista)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # E001 Strength(mg) 40			Reference Product Lot # 2 ND49M Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
10	58		20.9	54		27.8
20	95		2.3	94		6.4
30	95		1.6	97		2.5
45	96		1.5	97		3.5

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsule
10 mg, 20 mg, 40 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.

Sincerely yours,

/S/

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

6.1

#8

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-465 SPONSOR : Cheminor

DRUG AND DOSAGE FORM : Fluoxetine Hydrochloride Capsules

STRENGTH(S) : 10 mg, 20 mg, 40 mg

TYPES OF STUDIES : Fasting study on 40 mg capsule

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : The fasting study is acceptable.

DISSOLUTION : The dissolution testing was conducted by the USP method. The test product meets the USP specifications.

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 : Kuldeep R. Dhariwal BRANCH : II

INITIAL : KRD DATE : 11/8/00

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : /S/ DATE : 11/8/2000

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

INITIAL : /S/ DATE : 11/29/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, USP
10 mg, 20 mg, 40 mg
Study Amendment, 9/26/2000

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that dissolution testing as specified in USP 24, first supplement has been incorporated into your stability and quality control programs.

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 reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Fluoxetine Hydrochloride
10 mg, 20 mg and 40 mg Capsules
ANDA #75-465
Reviewer: Kuldeep R. Dhariwal
File name: 75465S.900

Reddy-Cheminor, Inc.
66 South Maple Avenue
Ridgewood, NJ 07450
Submission Date:
September 26, 2000

Review of an Amendment: Fasting Study on 40 mg Capsules

September 24, 1998: Fasting and non-fasting studies on 20 mg capsules, dissolution data and waiver request for 10 mg strength.
December 10, 1998: Biostudies and dissolution data were acceptable. Waiver for 10 mg capsule granted.
September 20, 1999: Waiver request for an additional strength, 40 mg.
November 16, 1999: The following deficiencies were communicated to the firm: If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.
March 30, 2000: The firm submitted the response to November 16, 1999 deficiencies. The firm was again requested to conduct a fasting study on its 40 mg capsules. The firm earlier conducted a non-fasting study on 20 mg capsule (dose 2x20 mg) for the approval of 20 mg strength and therefore a non-fasting study on 40 mg strength was not requested.
This submission: Fasting study on 40 mg capsules.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol #:	000632
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	
Study Dates:	Period I March 25, 2000
	Period II June 17, 2000

Analysis Dates: July 18 to July 31, 2000

Study Design: Randomized, two-way crossover design with a washout period of 12 weeks

Randomization Scheme: AB: 3,4,5,6,10,12,14,15,18,19,21,22,25
BA: 1,2,7,8,9,11,13,16,17,20,23,24,26

Treatments:

A= Fluoxetine Hydrochloride, 1x40 mg capsules; Cheminor Drugs; Batch #E001; Batch size: capsules; Manufacture Date: August 1999; Assay: %

B= Prozac®, 1x40 mg capsules; Lilly (Dista); Batch #2ND49M; Expiry Date: February 2001; Assay: %

Formulation of Test Product: Table 1

Subjects: 26 male subjects were enrolled according to the criteria specified in the protocol

Housing: From the evening before dosing until after the 36 hour blood draw

Dosing: After 10 hour fast, with 240 mL water

Sample Collection: Blood samples (10 mL) were collected at predose (0 h) and at following times after dosing:1,2,3,4,5,6,7,8,9,10,12, 24,36,48,60,72,84,96,120,144,168,336, 504 and 672 hours.

B. Study Results:

1. Clinical:

Drop-outs: Subject #13, 22, and 25 elected to withdraw after period I for personal reasons.

Adverse Events:

Subject	Complaint	Treatment	Relationship/Intensity
6	Erectile dysfunction, Headache	Test	Possible/Mild
7	Headache	Test	Possible/Mild
12	Difficulty to sleep	Test	Probable/Mild
16	Loose stool	Test	Possible/Moderate
19	Constipation, Loose stool, Dizziness, Nausea, Stomach cramps	Test	Probable/Mild
20	Headache	Test	Probable/Mild
25	Headache	Test	Probable/Mild
7	Headache	Reference	Probable/Mild
16	Loose stool	Reference	Possible/Mild
24	Headache	Reference	Probable/Mild

Protocol Deviations: There were a few sampling time deviations. The pharmacokinetic parameters were calculated using actual sampling times.

2. Analytical:

Method:
Internal Standard:
Linearity:

Regression:

Accuracy:

Precision:

Reassays:

The firm has provided following pre-study method validation results:

Linearity:

Accuracy:

Precision:

Recovery:

Stability:

3. Pharmacokinetics/Statistics:

FLUOXETINE:		
Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	91.41-104.31%
	$LAUC_{0-inf}$	90.71-104.09%
	LC_{max}	92.82-106.60%
Test/Reference Ratio:	AUC_{0-t}	0.99 (0.58-1.32)
	AUC_{0-inf}	0.99 (0.56-1.31)
	C_{max}	1.01 (0.59-1.33)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.95 (0.91-0.98)
	Reference	0.95 (0.81-0.98)
NORFLUOXETINE:		
Mean Plasma Concentrations:	Table 3 and Figure 2	
Pharmacokinetic Parameters:	Table 3	
90% Confidence Intervals:	$LAUC_{0-t}$	95.98-105.76%
	$LAUC_{0-inf}$	94.14-104.57%
	LC_{max}	94.53-102.66%
Test/Reference Ratio:	AUC_{0-t}	1.02 (0.75-1.35)
	AUC_{0-inf}	1.00 (0.76-1.42)
	C_{max}	0.99 (0.71-1.20)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.92 (0.67-0.99)
	Reference	0.91 (0.56-0.98)

Comments:

1. Fluoxetine: The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer. Norfluoxetine: The least squares means and 90% confidence intervals calculated by the reviewer are different than those reported by the firm:

	Firm	Reviewer
$LAUC_{0-t}$	95.3-105.3%	95.98-105.76%
$LAUC_{0-inf}$	93.5-104.0%	94.14-104.57%
LC_{max}	84.6-103.1%	94.53-102.66%

   The reviewer used two different SAS programs and got the same results. The study is acceptable either way.
2. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
3. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits. There was no

statistically significant period, sequence or treatment effect for any of these parameters.

4. The semi-log plots of the individual subject plasma concentrations are satisfactory. The firm has not submitted the linear plots of individual subject plasma concentrations. The DBE management decided that these graphs will not be requested unless they are absolutely required to complete the review. The review of the study can be completed without the linear plots.
5. The fasting study is acceptable.

In Vitro Dissolution Testing:

The dissolution testing was done using the USP method: 900 mL water, apparatus II (paddles) at 50 rpm. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence study. The test and reference products dissolve more than % in 30 minutes (Table 4).

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Cheminor Drugs on its fluoxetine hydrochloride capsules, 40 mg, lot #E001, comparing it to the reference product Prozac® capsules 40 mg, lot #2ND49M manufactured by Dista (Lilly) is acceptable to the Division of Bioequivalence. The study demonstrates that Cheminor's fluoxetine hydrochloride 40 mg capsule is bioequivalent to the reference product, Prozac® 40 mg capsule manufactured by Dista (Lilly).

2. The dissolution testing conducted by Cheminor on its fluoxetine hydrochloride 40 mg capsules is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL water at 37°C using apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % of the labeled amount of fluoxetine in the dosage form is dissolved in 30 minutes.

3. From the bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

/S/ 11/8/00
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 11/8/2000

Concur: /S/ Date 11/29/00
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

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Table 1

Comparative Formulation of Fluoxetine Capsules

Ingredient	Strength					
	10 mg		20 mg		40 mg	
	mg	%	mg	%	mg	%
Fluoxetine Hydrochloride	11.18*	5.08	22.36**	10.16	44.72***	10.16
Pregelatinized starch						
Total Fill Weight						

*equivalent to 10 mg fluoxetine, ** equivalent to 20 mg fluoxetine, *** equivalent to 40 mg fluoxetine

Hard gelatin capsule components: FD&C Blue #1, titanium dioxide, gelatin, silicon dioxide, sodium lauryl sulfate

10 mg: opaque light blue capsule imprinted "FLUOXETINE 10 mg" and "SHN"

20 mg: opaque light blue and light turquoise blue imprinted "FLUOXETINE 20 mg" and "SHN"

40 mg: opaque light blue and opaque white imprinted "FLUOXETINE" 40 mg" and "SHN"

Table 2

MEAN PLASMA FLUOXETINE LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=23

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.15	1.08	1.03	0.65	1.12
2	6.28	3.91	7.38	4.42	0.85
3	12.01	5.12	14.44	7.20	0.83
4	16.93	6.10	18.27	7.05	0.93
5	22.03	6.30	22.27	6.79	0.99
6	24.70	7.45	24.42	6.41	1.01
7	24.48	7.11	24.44	6.27	1.00
8	23.67	6.13	24.39	5.20	0.97
9	22.43	6.50	22.66	5.01	0.99
10	20.84	5.85	21.35	5.15	0.98
12	20.69	5.86	20.78	5.30	1.00
24	15.51	5.48	15.79	5.25	0.98
36	12.61	5.78	12.22	5.49	1.03
48	9.74	5.37	10.08	5.27	0.97
60	8.07	5.58	8.05	5.42	1.00
72	6.98	5.12	6.83	4.88	1.02
84	5.65	4.92	5.86	4.92	0.96
96	4.99	4.69	4.92	4.60	1.02
120	3.69	4.26	3.62	4.03	1.02
144	2.77	3.52	2.76	3.60	1.00
168	2.11	3.10	2.27	3.16	0.93
336	0.56	1.13	0.54	1.07	1.04
504	0.15	0.35	0.17	0.34	0.90
672	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1598.74	1256.58	1626.65	1218.36	0.98
AUCT	1525.91	1199.58	1548.96	1184.06	0.99
CMAX	26.35	7.48	26.23	6.18	1.00
KE	0.02	0.01	0.02	0.01	0.99
LAUCI	1285.76	0.63	1324.57	0.62	0.97
LAUCT	1227.03	0.63	1257.78	0.62	0.98
LCMAX	25.36	0.28	25.54	0.24	0.99
THALF	50.30	30.57	50.75	30.41	0.99
TMAX	6.83	0.94	7.17	1.37	0.95

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1611.17	1636.91	0.98	93.07	103.78
AUCT	1537.44	1558.92	0.99	94.00	103.24
CMAX	26.45	26.28	1.01	94.40	106.86
LAUCI	1292.17	1329.81	0.97	90.71	104.09
LAUCT	1232.97	1262.73	0.98	91.41	104.31
LCMAX	25.44	25.58	0.99	92.82	106.60

Table 3

MEAN PLASMA NORFLUOXETINE LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=23

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	1.29	0.90	1.52	1.03	0.85
3	2.79	1.68	3.46	1.99	0.81
4	4.51	2.36	5.04	2.96	0.90
5	6.28	3.09	6.41	3.31	0.98
6	7.85	3.96	7.78	3.71	1.01
7	8.47	3.85	8.56	3.93	0.99
8	9.04	4.32	9.39	4.69	0.96
9	9.01	4.23	9.41	4.69	0.96
10	9.31	4.29	9.88	4.90	0.94
12	10.71	4.72	10.91	5.45	0.98
24	11.88	5.11	12.30	5.64	0.97
36	15.77	6.33	15.63	7.33	1.01
48	14.29	5.36	14.98	6.86	0.95
60	15.68	5.90	15.59	6.25	1.01
72	15.70	5.76	15.95	6.41	0.98
84	15.93	5.49	16.23	6.22	0.98
96	14.90	5.02	15.02	5.52	0.99
120	13.94	4.91	13.81	4.93	1.01
144	13.05	4.53	12.98	4.51	1.01
168	11.47	3.77	12.37	4.56	0.93
336	6.26	2.83	5.72	2.54	1.09
504	2.92	2.20	2.79	1.95	1.05
672	1.27	1.44	1.33	1.58	0.96

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	5351.91	2094.79	5421.78	2266.67	0.99
AUCT	4869.26	1790.41	4853.04	1945.53	1.00
CMAX	17.11	6.12	17.59	7.16	0.97
KE	0.01	0.00	0.01	0.00	1.02
LAUCI	4917.93	0.44	4957.40	0.45	0.99
LAUCT	4502.78	0.43	4470.73	0.43	1.01
LCMAX	15.93	0.41	16.17	0.43	0.99
THALF	154.93	77.19	163.36	95.98	0.95
TMAX	63.65	26.20	78.80	33.12	0.81

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	5357.36	5426.13	0.99	93.13	104.34
AUCT	4869.19	4850.21	1.00	94.84	105.94
CMAX	17.08	17.55	0.97	91.69	102.93
LAUCI	4920.49	4959.44	0.99	94.14	104.57
LAUCT	4501.04	4467.31	1.01	95.98	105.76
LCMAX	15.89	16.13	0.99	94.53	102.66

Table 4. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 26, 2000
File Name: 75465S.900

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac®
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # E001 Strength(mg) 40			Reference Product Lot #2 ND49M Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
5	13		33.8	19		34.2
10	58		20.9	54		27.8
15	87		9.9	81		20.1
20	95		2.3	94		8.4
30	95		1.6	97		2.5
45	96		1.5	97		3.5

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

FIG 1. PLASMA FLUOXETINE LEVELS

FLUOXETINE HYDROCHLORIDE TABLETS, 40 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=1 X 40 MG

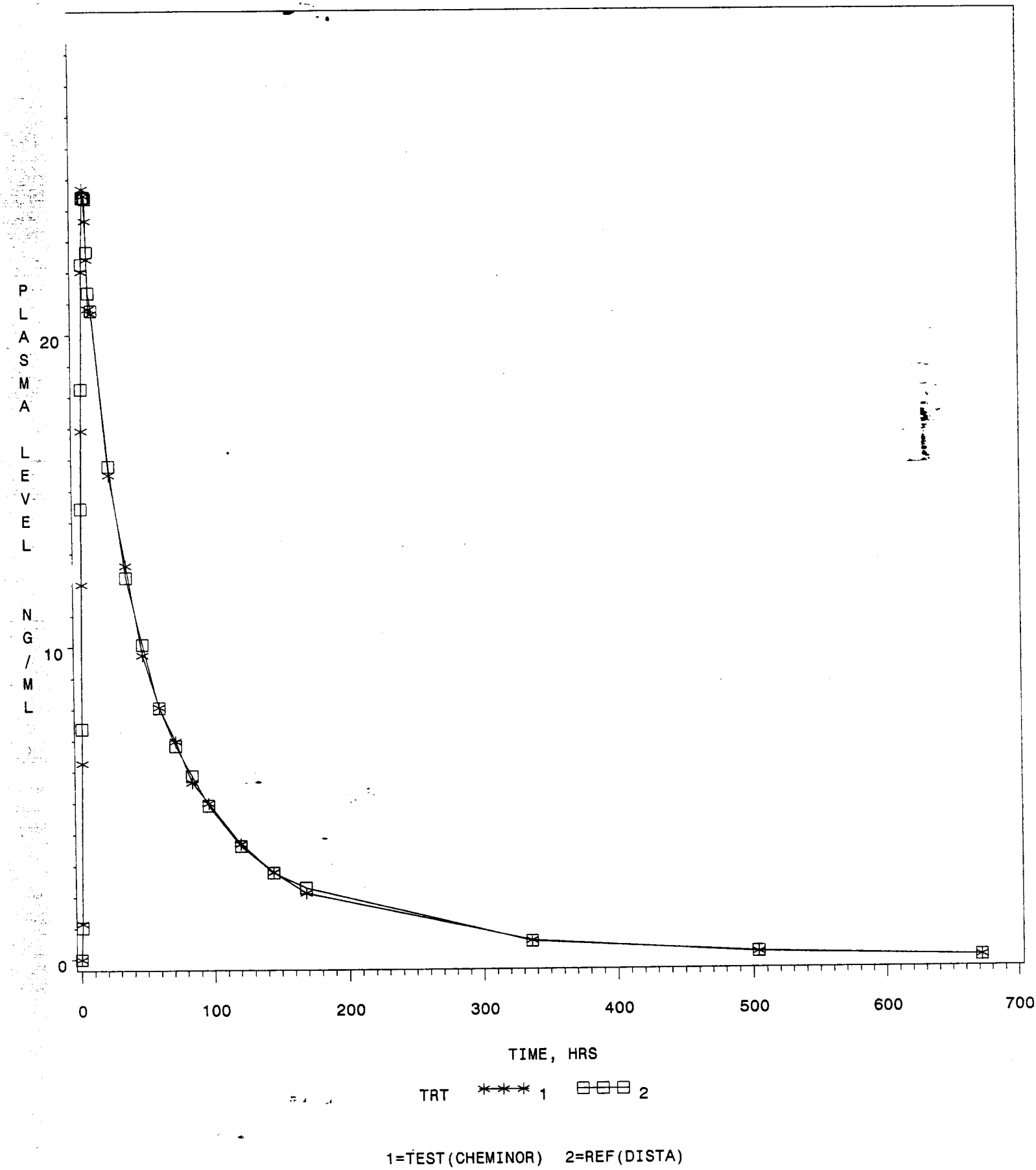
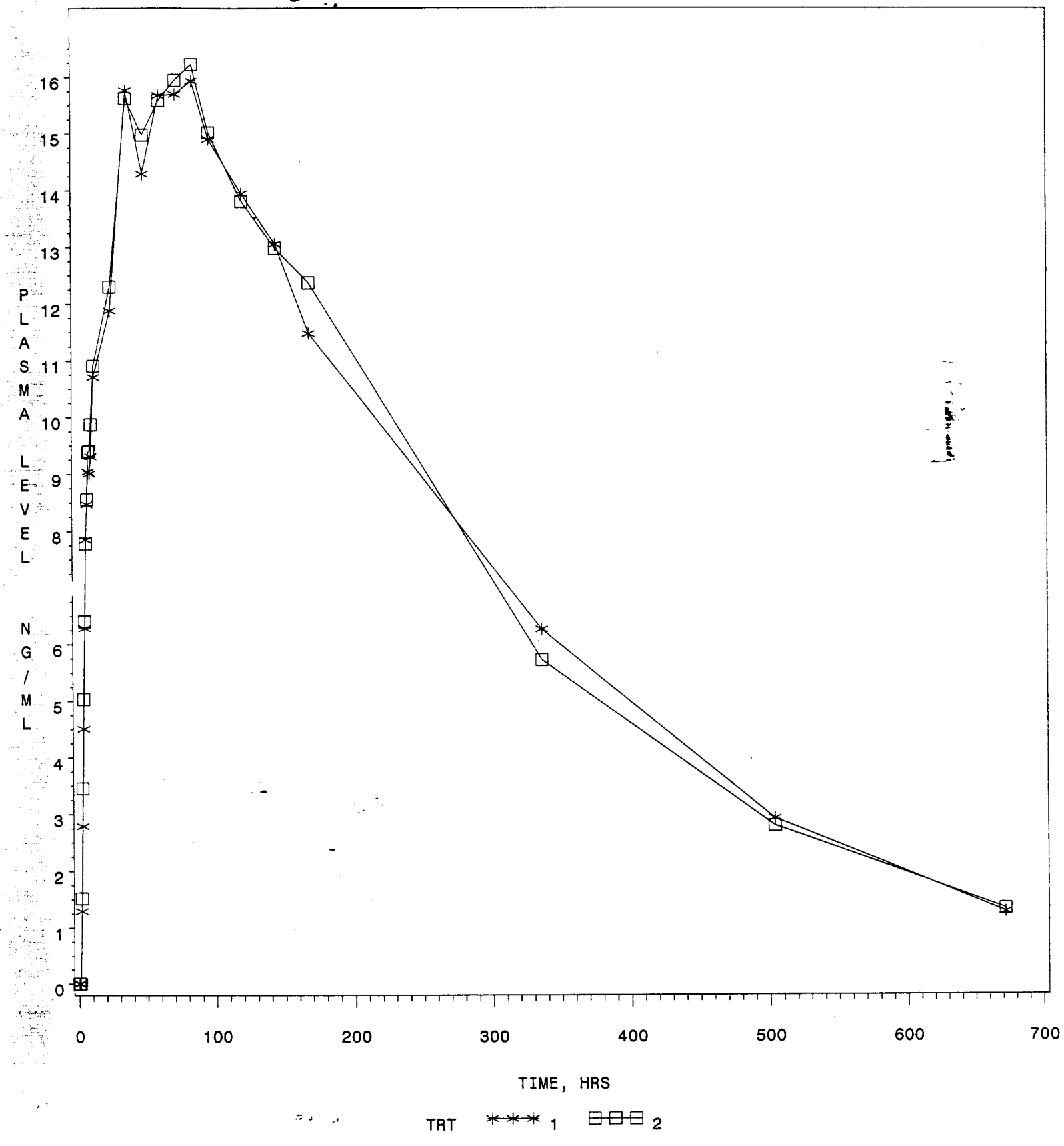


FIG 2. PLASMA NORFLUOXETINE LEVELS

FLUOXETINE HYDROCHLORIDE TABLETS, 40 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=1 X 40 MG



1=TEST(CHEMINOR) 2=REF(DISTA)