CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75049

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

9

ANDA # : 75-049 SPONSOR : Geneva

DRUG AND DOSAGE FORM : Fluoxetine HCl Capsules

STRENGTH(S) : 10 mg and 20 mg

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

Amendment for alternate source of active ingredient

STUDY SUMMARY : The waiver of *in vivo* bioequivalence requirements for fluoxetine hydrochloride capsules manufactured using alternate source of active ingredient is granted.

DISSOLUTION : 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 : 11/21/00

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : /S/ DATE : 12/9/2000

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

INITIAL : /S/ DATE : 12/12/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75049 APPLICANT: Geneva

DRUG PRODUCT: Fluoxetine HCl Capsules USP
10 mg and 20mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in first supplement, USP 24.

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

MARK

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75049 APPLICANT: Geneva Pharmaceuticals

DRUG PRODUCT: Fluoxetine Hydrochloride, 10 and 20 mg Capsules

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

Please acknowledge that the following dissolution testing specifications have been 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 Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-049 APPLICANT: Geneva

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, USP
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. Innovator's labeling states that fluoxetine's metabolism is not proportional to dose.

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

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 mg, 20 mg, 40 mg Capsules
ANDA #75049
Reviewer: Kuldeep R. Dhariwal
File name: V:\FIRMSAM\GENEVA\LTRS&REV\75049sdw.101

Geneva Pharmaceuticals
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038
Submission Date:
January 5, 2001

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

December 31, 1996: Fasting and non-fasting studies on 20 mg capsules, dissolution data and waiver request for 10 mg strength.
January 16, 1998: Biostudies and dissolution data were acceptable. Waiver for 10 mg capsule granted.
November 14, 2000: Waiver of *in vivo* bioequivalence study requirements for alternate source of active ingredient. The waiver was granted on December 20, 2000.
This submission: Waiver request for the 40 mg strength of fluoxetine capsules.

Reference Listed Drug: Prozac® by Lilly (Dista) available as:
Capsules 10 mg, 20 mg, 40 mg
Tablet 10 mg
Oral Solution 20 mg/5 mL

Geneva is requesting a biowaiver for 40 mg capsules based on the following:

- Acceptable bioequivalence studies on 20 mg capsules (dose 2x20 mg).
- The formulations for 10, 20 and 40 mg capsules are proportionally similar and the manufacturing process is the same.
- Dissolution data in 4 media (0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and water) support that Geneva's 40 mg capsules dissolve very similarly to Prozac® 40 mg capsules.

Comments: NOT TO BE RELEASED UNDER FOI

1. The reference 20 and 40 mg capsules are not proportionally formulated like the test 20 and 40 mg capsules.

2. [redacted] was denied the waiver for 40 mg strength in November 1999. The firm submitted a fasting study on 40 mg strength in November 2000.
3. In April 2000, [redacted] was informed that a waiver of ~~the~~ *in vivo* bioequivalence study cannot be granted for the 40 mg strength. The firm was requested to conduct a fasting study on the 40 mg capsule.
4. The DBE management in its meeting on May 1, 2000 discussed this issue and decided that the waiver for the 40 mg strength will be denied.

Recommendations:

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

/S/ 1/12/1
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 1/22/2001

Concur: /S/ Date 1/25/01
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

4/1
Amend

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75049 APPLICANT: Geneva

DRUG PRODUCT: Fluoxetine HCl Capsules USP
10 mg and 20mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in first supplement, USP 24.

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 and 20 mg Capsules
ANDA #75049
Reviewer: Kuldeep R. Dhariwal
File name: 75049SDW.N00

Geneva Pharmaceuticals
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038
Submission Date:
November 14, 2000

Review of an Amendment

Geneva has submitted an amendment to its tentatively approved ANDA for fluoxetine hydrochloride capsules USP, 10 mg and 20 mg. This supplement provides for an alternate source of the active drug substance, fluoxetine hydrochloride. The firm has submitted comparative dissolution profiles and is requesting a waiver of the *in vivo* bioequivalence requirements.

The proposed manufacturer and supplier of the active drug substance are:
Manufacturer:
Supplier:

The firm has manufactured fluoxetine hydrochloride capsules, 20 mg using the active ingredient from the alternate source (Lot #6498026, lot size: capsules).

The dissolution testing was done by the USP method: 900 mL water using apparatus II (paddle) at 50 rpm. The results are presented in Table 1.

F_2 test:

New test product vs. the original test product: 64.02
New test product vs. the innovator product: 61.79

Comments:

1. The dissolution profiles of the test product manufactured using the active ingredient from are comparable to that of the original test product and the innovator product. The test product meets the USP specifications. A value of 64.02 was obtained when F_2 test was applied between the two test lots, manufactured using active ingredient from the two different sources.

2. The firm has not provided the dissolution data for the 10 mg capsules manufactured using the active ingredient from the alternate source . For alternate source, the firm needs to manufacture only the strength used in the bioequivalence study and submit three months of stability data and comparative dissolution profile data (OGD procedure and policy guide #22-90). Therefore, the 10 mg strength does not need dissolution testing.
3. The formulation of the test 20 mg capsules manufactured using alternate source of active ingredient is same as that of the test capsules manufactured using active ingredient from (bio-lot).

Recommendations:

1. The waiver of *in vivo* bioequivalence study requirements for fluoxetine hydrochloride 20 mg capsules manufactured using alternate source of active ingredient is granted.
2. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37°C using apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

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

/S/

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

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 12/9/2002

Concur: /S/ Date 12/20/00
for Dale P. Conner, Pharm.D.

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg and 20 mg
ANDA No.: 75049
Firm: Geneva
Submission Date: November 14, 2000
File Name: \\CDS008\WP51F99\FIRMSAM\GENEVA\LTRS&REV\75049SDW.N00

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 (New lot) Lot #6498026 Strength(mg) 20			Reference Product Lot #1AP65A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	80		14	89		10.1
20	91		10.9	96		1.7
30	93		6.5	97		1.4
40	94		5.9	96		1.8

Sampling Times (Minutes)	Test Product (Bio-lot) Lot #6496022 Strength(mg) 20			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	90		1.7			
20	93		1.6			
30	94		1.1			
40	95		1.2			

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

9

ANDA # : 75-049 SPONSOR : Geneva

DRUG AND DOSAGE FORM : Fluoxetine HCl Capsules

STRENGTH(S) : 10 mg and 20 mg

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

Amendment for alternate source of active ingredient

STUDY SUMMARY : The waiver of *in vivo* bioequivalence requirements for fluoxetine hydrochloride capsules manufactured using alternate source of active ingredient is granted.

DISSOLUTION : 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 : 11/21/00

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : /S/ DATE : 12/9/2000

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

INITIAL : /S/ DATE : 12/12/00

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75049 SPONSOR: Geneva Pharmaceuticals
DRUG: Fluoxetine Hydrochloride
DOSAGE FORM: Capsules
STRENGTHS: 10 mg and 20 mg
TYPE OF STUDY: Single dose, Fasting and Nonfasting
STUDY SITE:

STUDY SUMMARY: Fasting Study: Forty-six subjects entered the study. Five subjects withdrew for personal reasons.
a) Fluoxetine: The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} are 96.6-107.7%, 96.7-105.7%, and 99.5-108.1% respectively. Subject #2 (ref drug), #27 (test drug) had several missing values and subject #42 had all values missing for period I (ref drug). The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} after omitting these subjects are 95.2-104.2%, 95.5-104.1%, and 98.4-106.5% respectively.
b) Norfluoxetine: The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} are 99.9-114.2%, 98.5-104.2%, and 96.6-102.6% respectively. Subject #12 (test drug), 3 and 16 (ref drug) had predose norfluoxetine concentrations. Subject #2 (ref drug), #27 (test drug) had several missing values and subject #42 had all values missing for period I (ref drug). The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} after omitting these subjects are 100.6-105.49%, 99.3-104.46%, and 96.5-103.19% respectively.
Nonfasting Study: Twenty-three subjects entered the study. Six subjects withdrew for personal reasons.
Fluoxetine and Norfluoxetine: Ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test nonfasting and reference nonfasting are within acceptable limits.

DISSOLUTION: The dissolution testing was done by FDA method: 900 mL water, apparatus II (paddles) at 50 rpm. The test products meet the specifications of NLT (Q) % in 30 minutes. The formulation for 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* bioequivalency requirements for 10 mg capsules is granted.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: /S/ DATE 1/16/98

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: /S/ DATE 1/16/1998

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: DPC DATE 1/16/98

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

1.1

Fluoxetine Hydrochloride
10 mg and 20 mg Capsules
ANDA #75049
Reviewer: Kuldeep R. Dhariwal
File name: 75049SDW.997

Geneva Pharmaceuticals
2555 W. Midway Blvd.
P.O.Box 446
Broomfield, CO 80038
Submission Date:
September 5, 1997

Response to Review of Bioequivalence Studies, Dissolution Data, and Waiver Request

Geneva previously submitted a single dose *in vivo* bioequivalence study under fasting and nonfasting conditions and dissolution data comparing its fluoxetine hydrochloride 20 mg capsules with Dista Pharmaceutical's (Lilly) Prozac® 20 mg capsules. The firm also requested for waiver of *in vivo* bioequivalence study requirements for its 10 mg capsules (File name: 75049SDW.D96). The study was found incomplete and the deficiency comments were sent to the firm. The firm submitted the response as amendment on September 5, 1997 which was assigned to this reviewer on January 7, 1998.

Response:

Comment 1: **As some samples in the nonfasting study were stored for 185 days before analysis, it will be necessary to document the stability of both fluoxetine and norfluoxetine, in frozen plasma samples during this time period.**

Response: Stability quality control samples were originally spiked on April 30, 1996 and stored at -22°C until analyzed on September 30, 1996 (150 days stability) and on August 6, 1997 (462 days stability). The firm had earlier submitted the stability data for 150 days and has now submitted the 462 days stability data in this amendment:

FLUOXETINE

Nominal conc.	Conc. after 462 days
1.51 ng/mL	1.488 ng/mL (CV:5.7%, n=9)
80.67 ng/mL	83.53 ng/mL (CV:10%, n=10)

NORFLUOXETINE

Nominal conc.	Conc. after 462 days
1.51 ng/mL	1.396 ng/mL (CV:9.6%, n=9)
80.40 ng/mL	79.347 ng/mL (CV:10.7%, n=10)

From the above data, it appears that fluoxetine and norfluoxetine are stable for 462 days when stored in human plasma at -22°C.

Comment 2: **Food study: Samples from subject #23 were run on two separate days; period I and II on Oct. 16, 1996 and period III samples were run on Nov. 8, 1996. Please note for future studies that all samples from one subject should be run on the same day.**

Response: acknowledges that for future studies, all samples from one subject should be run on the same day.

Comment 3: **None of the samples analyzed during the study had either fluoxetine or norfluoxetine plasma concentrations higher than ng/mL. Most of the samples were between ng/mL for fluoxetine, and between ng/mL for norfluoxetine. The laboratory used the standard curve of 0.50-100 ng/mL, and the following QC sample concentrations: low ng/mL, medium 40 ng/mL, and high ng/mL. In the future, the concentrations of the quality control samples should be chosen within and/or much closer to the concentration range of the actual plasma concentration of the drug.**

Response: acknowledges that for future studies, QC samples should be chosen that are closer to the concentration range of the actual plasma concentrations of the drug.

Comment 4: **The waiver request for the 10 mg capsule cannot be granted at this time. A response to item 1 is required. Please resubmit the waiver request for the 10 mg capsule along with the response to deficiency #1 above.**

Response: ~~We request~~ that any requirement for separate, additional, *in vivo* bioavailability/bioequivalency studies on fluoxetine capsules 10 mg, be waived and the bioavailability/ bioequivalence requirement for this product be considered as fulfilled.

Comments:

1. The firm has shown that fluoxetine and norfluoxetine are stable in plasma stored at -22°C for 462 days. The plasma samples in nonfasting study were stored for a maximum period of 185 days.

2. The firm has satisfactorily responded to all the deficiencies.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Geneva Pharmaceuticals on its fluoxetine hydrochloride capsules, 20 mg, lot #6496022, comparing it to the reference product Prozac® capsules 20 mg, lot #9AP49A manufactured by Dista (Lilly) has been found acceptable by the Division of Bioequivalence. The study demonstrates that Geneva'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 Geneva Pharmaceuticals on its fluoxetine hydrochloride capsules 20 mg, lot #6496022, comparing it to the reference product Prozac® capsules 20 mg, lot #9AP49A manufactured by Dista (Lilly) has been found acceptable by the Division of Bioequivalence. The study demonstrates that under nonfasting conditions, the bioavailability of Geneva's fluoxetine hydrochloride 20 mg capsules is similar to the reference product Prozac® 20 mg capsule manufactured by Dista (Lilly).

3. The dissolution testing conducted by Geneva 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 the *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/ 1/16/98

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

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 1/16/1998

Concur: /S/ Date 1/16/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Draft: 010998; Final: 011698

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75049 APPLICANT: Geneva Pharmaceuticals

DRUG PRODUCT: Fluoxetine Hydrochloride, 10 and 20 mg Capsules

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

Please acknowledge that the following dissolution testing specifications have been 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 Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 17 1997

Fluoxetine Hydrochloride
10 mg and 20 mg Capsules
ANDA #75049
Reviewer: Kuldeep R. Dhariwal
Filename: 75049SDW.D96

Geneva Pharmaceuticals
2555 W. Midway Blvd.
P.O.Box 446
Broomfield, CO 80038
Submission Date:
December 31, 1996

Review of Fasting and Fed Bioequivalence Studies, Dissolution Data and Waiver Request

The firm has submitted single dose bioequivalence studies under fasting and fed 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 (±)-N-methyl-3-phenyl-3-[(∝,∝,∝-trifluoro-p-tolyl)oxy]propylamine hydrochloride. The antidepressant action of fluoxetine is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. 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 (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.

Bioavailability of Fluoxetine Capsules, 20 mg Under Fasting Conditions:

A. Objective:

The objective of this study was to compare the bioavailability of Geneva and Dista (Lilly) 20 mg fluoxetine hydrochloride capsules following administration of a 40 mg dose under fasting conditions.

B. Study Sites and Investigators:

Clinical Site:
Analytical Site:
Principal Investigator:
Protocol #960380 "Comparative, randomized, single-dose, 2-way crossover bioavailability study of Geneva and Dista (Prozac®) 20 mg fluoxetine hydrochloride capsules (Pulvules) in healthy adult males under fasting conditions following administration of a 40 mg dose' was approved by the Institutional Review Board, Inc.
Consent Form: A copy of the volunteer informed consent form used in the study is given in vol. 1.1 IRB/Consent section.
Study Dates: Period I June 1, 1996
Period II July 27, 1996
Analysis Dates: September 9 to October 21, 1996

C. Study Design:

The study was designed as a two-way, single-dose, open-label, two-treatment crossover study with a washout period of 8 weeks. The subjects were housed for 12 hours prior to dosing and until 36 hour blood draw. The subjects were assigned as follows:

Sequence	Subject number	Period I	Period II
1	1,2,3,5,8,9,11,14,16,17,18, 21,23,25,26,29,30,31,33,37, 38,40,44,45	A	B
2	4,6,7,10,12,13,15,19,20,22, 24,27,28,32,34,35,36,39,41, 42,43,46	B	A

Subject numbers 4,8,9,18 and 46 did not complete the study.

A = Fluoxetine Hydrochloride, 2x20 mg capsules; Geneva Pharmaceuticals; Lot # 6496022; Lot size: Theoretical Yield capsules, Actual Yield capsules; Manufacture Date: April 1996; Assay: %; Content Uniformity: %

B = Prozac®, 2x20 mg capsules; Dista Pharmaceutical; Lot #9AP49A; Expiry Date: Nov. 1998; Assay: %; Content Uniformity: %

Formulation of the test product is given in Table 1.

The subjects fasted for 10 hours prior to dosing and until 4 hours postdose. Water was permitted freely except within 1 hour of dosing. The dose was administered with 240 mL of water.

D. Subject Selection:

Forty-six healthy, adult, male volunteers were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-45 years of age, weighing at least 60 Kg, and are within 15% of their ideal weights
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits

Subjects were excluded from the study based on the following criteria:

- history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease
- history or presence of alcoholism or drug abuse
- hypersensitivity or idiosyncratic reaction to fluoxetine
- subjects receiving monoamine oxidase inhibitors within 30 days prior to dosing
- subjects on an abnormal diet for whatever reason during the 4 weeks prior to study
- participation in a clinical trial within 28 days of study start
- donation of blood through completion of study in excess of 500

mL in 14-days, 750 mL in 3 months, 1 L in 6 months, 1.5 L in 9 months or 2 L in a year

Subjects were imposed with following restrictions:

- no medication including OTC products (vitamins excluded) for 7 days prior to study
- no alcohol or caffeine-containing foods and beverages 24 hours prior to and during sample collection

E. Sample Collection:

Blood samples were drawn into Vacutainers containing EDTA prior to drug administration (2x10 mL) and at the following times after drug administration (1x10 mL): 1,2,3,4,5,6,7,8,10,12,16,24,36,48, 60, 72, 96, 120, 144, 168, 336, 504 and 672 hours. Blood samples were cooled in an ice bath and centrifuged under refrigeration as soon as possible. Plasma was separated and stored at -12°C. Samples were transferred to analytical site on dry ice where they were stored at -22°C.

F. Analytical Methods:

ACCEPTANCE CRITERIA: Calibration samples (QCs and standards) were analyzed along with each batch of study samples. A curve was acceptable if `r' value was 0.990 or better. Four of the six QC samples must be evaluable including at least one at each concentration and they should be within % of nominal concentration for high and medium concentrations and % of nominal concentration for low concentration.

G. Pharmacokinetics/Statistics:

AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{1/2}$, and KEL were calculated. Analysis of variance was performed on these pharmacokinetic parameters. The analysis of variance model sequence, subjects nested within sequence, period and drug formulation as factors was used. The analysis of variance included calculations of least squares means, adjusted differences between formulation means and the standard error associated with these differences. Two one-sided test for bioequivalence, 90% confidence intervals for the difference between drug formulation least-squares means were calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max} using untransformed and log-transformed data.

H. Results:

1. Clinical:

Forty-six subjects entered the study. Subject numbers 4,8,9,18, and 46 withdrew for personal reasons in period I.

Adverse events:

Following adverse reactions are reported:

DRUG RELATED: 2 EVENTS

Headache (2 episodes) reference drug

NOT DRUG RELATED: 18 EVENTS

Test Drug:

Common Cold (2 episodes)
Sore throat (1 episode)
Headache (1 episode)
Sinus Infection (1 episode)
Lightheaded (1 episode)
Sharp pain in right arm (1 episode)

Reference Drug:

Headache (3 episodes)
Esophageal reflux (1 episode)
Food poisoning (1 episode)
Allergies (1 episode)
Pain in lower back (1 episode)
Fainted (1 episode)
Vomiting (1 episode)
Stomach ache (1 episode)
Body ache (1 episode)

In addition, subject #28 felt faint soon after 2 hour blood draw in period I (reference drug).

The following subjects received medications during the study:

subject #	Medication
3	amoxicillin (7x250 mg) during period I
11	amoxicillin (4x500 mg) per day for 6 days (31-36 days after period I dosing) for acute sinusitis
15	aspirin (6x325 mg) during wash-out period
19	Sudafed (2x30 mg pesudoephedrine) 6 hrs prior to period II dosing for allergic rhinitis

43	Benadryl cream for poison ivy
46	Tylenol (3x500 mg) 21 days postdose, 4x500 mg everyday between 22 and 29 days postdose and ibuprofen (12x200 mg) 27 days postdose in period I
16	Tylenol (2x325 mg) 6 hours after period I dosing

Deviations in the study:

Protocol deviations:

1. Some subjects received medications during the study as detailed above.
2. Subjects did not consume alcohol or xanthine containing products until 168 hours after dosing and 24 hours prior to 336, 504, and 672 hours postdose with the following exceptions:

Period I	Subject #	
I	15	beer between 168 and 336 hours and 2 twelve oz. cans of beer between 504 and 672 hours
	21	one sip of Pepsi between 504 and 672 hours
II	15	4 oz. of coffee between 144 and 168 hours
	31	8 oz. of coffee between 72 and 96 hours
	43	Mountain Dew between 120 and 144 hours

3. Deviations in scheduled phlebotomy times: Several deviations in scheduled phlebotomy times were reported (see attached tables). Actual blood collection times were used for PK calculations.

4. Reassays: Following samples were reassayed for the reasons shown against them:

FLUOXETINE:

# of samples	reason for reassay
3	poor chromatography
10	lost in processing
32	anomalous sample value
32	no sample

NORFLUOXETINE:

# of samples	reason for reassay
4	poor chromatography

2	not reportable
11	lost in processing
32	no sample
36	anomalous sample value

2. Analytical:

SPECIFICITY: Human plasma used to prepare calibration standards and quality control samples were chromatographically screened for interfering substances prior to use. During sample analysis, a predose sample from each subject was extracted with internal standard to detect interference from contaminants at the retention times of fluoxetine and norfluoxetine. The zero hour samples in period II of subject numbers 2,7,24,31 and 38 showed interferences at the retention times of norfluoxetine of approximately 31.6%, 51.7%, 60.7%, 30.8% and 78.3% of the LLOQ respectively.

LINEARITY: The range of quantification for fluoxetine was ng/mL. The range of quantification for norfluoxetine was ng/mL. The coefficients of determination of the calibration lines for fluoxetine was 0.998 or better and for norfluoxetine was 0.994 or better. Quality control samples at three different concentrations (Fluoxetine 1.51, 40.27, and 80.53 ng/mL; Norfluoxetine 1.49, 39.64, and 79.27 ng/mL) were run with each data set.

SENSITIVITY: The lower limit of quantification for fluoxetine and norfluoxetine was 0.51 ng/mL and 0.50 ng/mL respectively.

INTERNAL STANDARD: Diphenhydramine

ACCURACY:
Fluoxetine: Standards 96.9-106.2%, QC samples %
Norfluoxetine: Standards 96.7-105.0%, QC samples %

PRECISION:
Fluoxetine: Standards 2.1-8.1%, QC samples %
Norfluoxetine: Standards 4.9-9.5%, QC samples %

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

SPECIFICITY: Human plasma, analytes and internal standards were screened for interfering substances before use. No significant interference with the analytes or internal standard was observed in 14 of the 15 blank plasma pools screened.

STANDARD curve range: Fluoxetine ng/mL
Norfluoxetine ng/mL

The lower limit of quantification was set at ng/mL for both analytes. The between-run coefficient of variation for QC samples at this concentration was % for fluoxetine and % for norfluoxetine.

ACCURACY:
Fluoxetine: Standards: 93.1-105.2%
QC samples: Between-run %
Within-run %
Norfluoxetine: Standards: 98.6-101.8%
QC samples: Between-run %
Within-run %

PRECISION:
Fluoxetine: Standards: 2.1-7.5%
QC samples: Between-run %
Within-run %
Norfluoxetine: Standards: 2.8-9.9%
QC samples: Between-run %
Within-run %

RECOVERY:
The absolute recoveries were performed on QC samples at three different concentrations by comparing analytical results from an unextracted calibration curve:

Fluoxetine:	1.51 ng/mL	%
	40.34 ng/mL	%
	80.67 ng/mL	%
Norfluoxetine:	1.51 ng/mL	%
	40.20 ng/mL	%
	80.40 ng/mL	%

Internal Standard: The recovery was calculated by comparing a prepared calibration curve (pure standards) injected with blank plasma prepared with ng/mL of diphenhydramine. The mean % recovery was 90.89%.

STABILITY:
a) Long-term stability: Replicates of stability samples stored at -22°C for designated time were analyzed with freshly spiked comparison samples. The results show that the samples were stable for 150 days.
Note: Samples in the present study were stored for less than 150 days.
b) Short-term stability: The results show that the samples are stable for 10.38 hours when left on bench at room temperature (20°C).
c) Stability of extracted samples: Samples were extracted, reconstituted and kept either at room temperature or at 4°C. They were compared with freshly thawed and then extracted comparison samples. The results show that the samples when kept in reconstitution solvent were stable for 21.6 hours at 4°C and for 40.7 hours at room temperature.

d) Freeze-thaw stability: Samples were stable after three freeze-thaw cycles.
e) Autosampler stability: Fluoxetine and norfluoxetine were stable for 3.2 hours in autosampler at 20°C.

3. Pharmacokinetics/Statistics:

Fluoxetine:

The mean plasma concentrations of fluoxetine at each time point after test and reference products are shown in Table 2. The time courses of fluoxetine concentrations after the two products are plotted in Figures 1 and 2. The pharmacokinetic parameters are shown in Tables 2 and 3. AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test product were about 3-4% higher than that of reference product. The T_{max} in test product occurred about 28 minutes earlier than in the reference product.

The individual ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 4. The test/reference ratio for AUC_{0-t} ranged from (mean 1.04), AUC_{0-inf} ranged from (mean 1.02), and for C_{max} ranged from with a mean of 1.04.

Table 5 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from (one subject had 0.757 ratio) for test and (one subject had 0.475 ratio) for reference product.

The 90% confidence intervals are within the acceptable range of %. There was no statistically significant period, sequence, or treatment effect for AUC_{0-t} and AUC_{0-inf}. However, there was significant treatment (p=0.0451) and sequence (p=0.0899) effect for C_{max} but not for log transformed C_{max}.

Norfluoxetine:

The mean plasma concentrations of norfluoxetine at each time point after test and reference products are shown in Table 6. The time courses of norfluoxetine concentration after the two products are plotted in Figures 3 and 4. The pharmacokinetic parameters are shown in Tables 6 and 7. AUC_{0-t} and C_{max} of the test and reference products differed by less than 3%. AUC_{0-inf} differed by about 12%. The T_{max} in the test product occurred about 7 hours later than in the reference product.

The individual ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 8. The test/reference ratio for AUC_{0-t} ranged from (mean 1.12, one subject's ratio was 4.59), AUC_{0-inf} ranged from (mean 1.02), and for C_{max} ranged from with a mean of 1.00.

Table 9 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from for test and from for reference product.

The 90% confidence intervals are within the acceptable limits of 80-125%. There was statistically significant treatment effect for AUC_{0-t} (0.0289).

Bioavailability of Fluoxetine Hydrochloride, 20 mg Capsules Under Fed Conditions:

A. Objective:

To compare the bioavailability of Geneva and Dista 20 mg fluoxetine hydrochloride capsules under fed conditions and to compare the bioavailability of Geneva product under fed and fasting conditions.

B. Study Sites and Investigators: Same as for fasting study

Protocol #960379 `Comparative, randomized, single-dose, 3-way crossover bioavailability study of Geneva and Dista 20 mg fluoxetine hydrochloride capsules in healthy adult males under fed and fasting conditions following administration of a 40 mg dose' was approved by Institutional Review Board, Inc.
Consent Form: A copy of the volunteer informed consent form used in the study is attached in vol. 1.7, IRB/Consent section.

Study Dates: Period I May 11, 1996
Period II July 6, 1996
Period III August 31, 1996

Analysis Dates: October 3 to November 12, 1996

C. Study Design:

The study was designed as a randomized, three treatment, single-dose, open-label study. The study was executed in three phases with eight weeks wash out period between doses. Twenty-three healthy male subjects were enrolled and were assigned as follows:

Subject #	Period I	Period II	Period III
1,2,8,16	B	C	A
3,6,18,22	A	B	C
4,14,20,21	C	A	B
5,9,11,23	A	C	B
7,12,15	B	A	C
10,13,17,19	C	B	A

Subject numbers 3,11,14,17,19, and 21 did not complete the study.

A= Fluoxetine Hydrochloride capsules, 2x20 mg; Geneva Pharmaceuticals; Lot #6496022; Manufacture Date: April 1996; administered after an overnight fast

B= Fluoxetine Hydrochloride capsules, 2x20 mg; Geneva Pharmaceuticals; Lot #6496022; Manufacture Date: April, 1996; administered 30 minutes after a standard breakfast

C= Prozac® capsules, 2x20 mg; Dista Pharmaceuticals (Lilly); Lot #9AP49A; Expiry Date: November 1998; administered 30 minutes after a standard meal

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

D. Subject Selection:

Twenty-three adult male subjects were enrolled in the study with essentially same inclusion and exclusion criteria as in the fasting study. They were subjected to same screening procedure and restrictions.

E. Study Procedure:

Treatment A: Subjects were given a single oral dose of 2x20 mg of the assigned formulation with 240 mL of water after an overnight fast.

Treatments B and C: After an overnight fast and 30 minutes before their scheduled dosing times, subjects were given a standardized breakfast. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 rasher of Canadian bacon, 4 oz. hash brown potatoes, 180 mL of orange juice and 240 mL whole milk. The dose (2x20 mg) was given with 240 mL of water.

F. Sample collection, Analytical Methods, and Pharmacokinetics/ Statistical Analysis:

Blood samples were collected at 0 (predose), 1,2,3,4,5,6,8,10,12, 16, 24, 36, 48, 60, 72, 96, 120, 144, 168, 336, 504 and 672 hours. Analytical methods and statistical analysis used in the study were same as for fasting study.

G. Results:

1. Clinical:

Twenty-three subjects entered the study. Subject numbers 3 and 21 withdrew prior to period II dosing and subject numbers 11,14,17, and 19 withdrew prior to period III dosing due to personal reasons. Thus, seventeen subjects completed the study.

Adverse events: Following non-drug related medical events are reported:

Treatment A: Headache (1 episode)
Bowels had not moved as per usual (1 episode)
Gastritis (1 episode)
Inflammation of esophagus (1 episode)
Treatment B: Headache (2 episodes)
Poison Ivy (1 episode)
Treatment C: Headache (2 episodes)
Sutures on forearm (1 episode)
Bump on forehead (1 episode)

The following subjects required medication to alleviate the discomfort associated with medical events:

Subject #15 took cimetidine (300 mg) from approximately 33-45 days after period II dosing for gastritis. Subject #1 applied Ivy Rest® topically to poison ivy between the 504 and 672 hour blood draws in period I.

Deviations in the study:

a) Protocol deviations:
1. Subject #4 took 2 Tylenol tablets approx. 4 days preceding period I dosing.
2. In period I, subject numbers 1 and 2 received the standard breakfast 32.8 minutes instead of 30 minutes prior to dosing. In addition, these subjects also ate 1 oz. of fruit danish and 6 oz. of orange juice.
3. In period I, subject #4 received standard breakfast 31.8 minutes instead of 30 minutes prior to dosing.
4. Several subjects consumed beer, coffee, soda, cookies etc during the course of the study (see attached table).
b) Blood sampling deviations: Several deviations in scheduled phlebotomy times were reported (see attached table). Actual blood collection times were used for PK calculations.

Reassays: Following samples were reassayed for the reasons shown against them:

Fluoxetine:

# of samples	reason for reassay
7	anomalous sample value
17	lost in processing

Norfluoxetine:

# of samples	reason for reassay
6	anomalous value
2	not reportable
5	poor chromatography
18	lost in processing

2. Analytical:

SPECIFICITY: One predose sample showed interference of 48.8% at the retention time of fluoxetine. Two predose samples showed interferences of 79.1% and 33.3% at the retention time of norfluoxetine.

ACCURACY: Inter-run

Fluoxetine: Standards: 97.1-105.9%
QC samples: %
Norfluoxetine: Standards: 92.3-109.1%
QC samples: %

PRECISION: Inter-run

Fluoxetine: Standards: 3.0-7.3%
QC samples: %
Norfluoxetine: Standards: 4.0-8.5%
QC samples: %

STABILITY: The study samples were stored for a period not exceeding 185 days. The firm documents the stability of fluoxetine and norfluoxetine in plasma at -22°C for 150 days.

SENSITIVITY: The lower limit of quantitation for fluoxetine was ng/mL and for norfluoxetine was ng/mL. Correlation coefficients were greater than for fluoxetine and for norfluoxetine.

3. Pharmacokinetics/Statistics:

Fluoxetine:

The mean plasma concentrations of fluoxetine measured at each time point is given in Table 10. The time courses of fluoxetine concentration after the three treatments are given in Figures 5 and 6.

When the test and reference formulations were administered after a meal, the arithmetic means for AUC_{0-t} and AUC_{0-inf} were almost the same. The mean C_{max} of the test product was 2% lower than that of the reference product and occurred about 54 minutes earlier.

The arithmetic means for AUC_{0-t} and AUC_{0-inf} were 8% and 10% respectively lower in test fasted compared to test fed. The C_{max} in test fasted was 8% higher compared to test fed and occurred about 50 minutes earlier.

Following are the ratios of the means of the pharmacokinetic parameters:

Test-fed/Ref-fed

Parameter	Ratio of Arithmetic Means	Ratio of Geometric Means
AUC_{0-t}	0.990	0.975
AUC_{0-inf}	0.998	0.981
C_{max}	0.976	0.977

Test-fed/Test-fast

AUC_{0-t}	1.089	1.005
AUC_{0-inf}	1.106	1.015
C_{max}	0.920	0.906

Norfluoxetine:

The mean plasma concentrations of norfluoxetine measured at each time point is given in Table 11. The time courses of norfluoxetine concentration after the three treatments are given in Figures 7 and 8.

When the test and reference formulations were administered after a meal, the arithmetic means for AUC_{0-t} of the test product were 4% lower than the reference product. The arithmetic means for AUC_{0-inf} were almost the same for test fed and reference fed. The mean C_{max} of the test product was 6% lower than that of the reference product and occurred about 2 hours later.

The arithmetic means for AUC_{0-t} and AUC_{0-inf} were 15 and 11% respectively higher in test-fasted compared to test-fed. The mean C_{max} in test-fed was 12% lower compared to test-fasted subjects and occurred at the same time.

Following are the ratios of the means of the pharmacokinetic parameters:

Test-fed/Ref-fed

Parameter	Ratio of Arithmetic Means	Ratio of Geometric Means
AUC_{0-t}	0.959	0.943
AUC_{0-inf}	0.994	0.994
C_{max}	0.940	0.947

Test-fed/Test-fast

AUC_{0-t}	0.869	0.846
AUC_{0-inf}	0.899	0.892
C_{max}	0.887	0.855

In Vitro Dissolution Testing:

The firm has submitted comparative dissolution data for test and reference products. 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 12). Two of the twelve 10 mg reference capsules dissolved less than % (% and %) at 30 minutes.

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 except for pregelatinized starch. The amount of pregelatinized starch is adjusted to account for the difference in the amount of active ingredient between the two strengths.

Comments:

Analytical:

1. The firm has not documented the stability of fluoxetine and norfluoxetine in frozen plasma samples for 185 days. Some samples in food study were stored for this period.

2. None of the samples analyzed during the study had fluoxetine or norfluoxetine plasma concentrations higher than ng/mL. Most of the samples were between ng/mL for fluoxetine and between ng/mL for norfluoxetine. The firm has used the standard curve of 0.50-100 ng/mL and these QC sample concentrations: low ng/mL, medium 40 ng/mL, and high ng/mL.

Fasting Study:

Forty-six subjects entered the study. Subject numbers 4,8,9,18, and 46 withdrew for personal reasons. Forty-one subjects completed the study. There were two drug related and eighteen other adverse events. Some subjects received medications like amoxicillin, Tylenol, Sudafed, aspirin, ibuprofen during the study. Several deviations in scheduled phlebotomy times were reported. Actual blood collection times were used for calculations.

FLUOXETINE:

1. AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test product were about 3-4% higher than that of the reference product. The T_{max} in the test product was 28 minutes earlier than the reference product.

2. The 90% confidence intervals are within the acceptable limits of %. There was no statistically significant period, sequence, or treatment effect for AUC_{0-t} and AUC_{0-inf}. However, there was significant treatment (p=0.0451) and sequence (p=0.0899) effect for C_{max} but not for log transformed C_{max}.

3. Subject #2 (reference drug), #27 (test drug) had several missing values and subject #42 had all values missing for period I (reference drug) due to interference at the retention time of the internal standard. This reviewer repeated statistical analysis of the data after eliminating these three subjects. The following 90% confidence intervals were obtained:

$LNAUC_{0-t}$	95.18-104.21%
$LNAUC_{0-inf}$	95.53-104.13%
LNC_{max}	98.36-106.54%

NORFLUOXETINE:

1. AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test and reference products differed by less than 3%. The T_{max} in the test product was about 7 hours later than in the reference product.

2. The 90% confidence intervals are within the acceptable limits of % . There was statistically significant treatment effect for AUC_{0-t} (0.0289).

3. Subject #12 (test drug), 3 and 16 (reference drug) had predose (0 hour) norfluoxetine plasma concentrations of 0.78, 1.21, and 0.61 ng/mL respectively in period II. In addition, subject #2 (reference drug), 27 (test drug) had several missing values and subject #42 had all values missing for period I (reference drug). This reviewer repeated statistical analysis of the data after eliminating these subjects (#2,3,12,16,27 and 42). The following 90% confidence intervals were obtained:

$LNAUC_{0-t}$	100.60-105.49%
$LNAUC_{0-inf}$	99.30-104.46%
LNC_{max}	96.52-103.19%

4. The reviewer repeated pharmacokinetic and statistical analysis of the data. In general, there was good agreement between the reviewer's and firm's calculations.

Food Study:

Twenty-three subjects entered the study. Subject numbers 3 and 21 withdrew prior to period II dosing and subject numbers 11, 14, 17 and 19 withdrew prior to period III dosing due to personal reasons. Seventeen subjects completed the study. As per the protocol, statistical and pharmacokinetic analyses were performed using data from subjects who completed at least two periods of the study. One subject took cimetidine (300 mg) from approximately 33-45 days after period II dosing for gastritis. Several deviations in scheduled phlebotomy times were reported. Actual blood collection times were used for PK calculations.

FLUOXETINE:

1. Following are the ratios of the means of the PK parameters:

Test-fed/Ref-fed

Parameter	Ratio of Arithmetic Means	Ratio of Geometric Means
AUC_{0-t}	0.990	0.975
AUC_{0-inf}	0.998	0.981
C_{max}	0.976	0.977

Test-fed/Test-fast

AUC_{0-t}	1.089	1.005
AUC_{0-inf}	1.106	1.015
C_{max}	0.920	0.906

2. Subject numbers 11 and 14 did not complete period III (test-fed) and therefore the reviewer dropped the data from these subjects for ref-fed. The following ratios were obtained based on arithmetic means:

Parameter	Test-fed/Ref-fed
AUC_{0-t}	1.01
AUC_{0-inf}	1.00
C_{max}	1.00

3. Subject numbers 17 and 19 did not complete test-fast period and therefore this reviewer eliminated the data from these subjects for test-fed period. Similarly, subject numbers 11 and 14 did not complete test-fed period and therefore the data from these subjects were eliminated for test-fast period. The following ratios were obtained based on arithmetic means:

Parameter	Test-fed/Test-fast
AUC_{0-t}	0.99
AUC_{0-inf}	1.00
C_{max}	0.98

NORFLUOXETINE:

1. Following are the ratios of the means of the pharmacokinetic parameters:

Test-fed/Ref-fed

Parameter	Ratio of Arithmetic Means	Ratio of Geometric Means
AUC_{0-t}	0.959	0.943
AUC_{0-inf}	0.994	0.994
C_{max}	0.940	0.947

Test-fed/Test-fast

AUC_{0-t}	0.869	0.846
AUC_{0-inf}	0.899	0.892
C_{max}	0.887	0.855

2. Subject numbers 11 and 14 did not complete period III (test-fed) and therefore the reviewer dropped the data from these subjects for ref-fed. The following ratios were obtained based on arithmetic means:

Parameter	Test-fed/Ref-fed
AUC_{0-t}	0.97
AUC_{0-inf}	1.00
C_{max}	0.95

3. Subject numbers 17 and 19 did not complete test-fast period and therefore this reviewer eliminated the data from these subjects for test-fed period. Similarly, subject numbers 11 and 14 did not complete test-fed period and therefore the data from these subjects were eliminated for test-fast period. The following ratios were obtained based on arithmetic means:

Parameter	Test-fed/Test-fast
AUC_{0-t}	0.92
AUC_{0-inf}	0.94
C_{max}	0.96

Dissolution:

The dissolution testing was done by FDA method. The firm has demonstrated that test products dissolve more than % in 30 minutes. The *in vitro* dissolution data are acceptable.

Waiver:

1. The 10 mg capsules are proportionally similar in their active and inactive ingredients to 20 mg capsules.

2. The dissolution data are acceptable. The test products meet the specifications. The waiver can be granted.

Deficiency:

1. Please document the stability of fluoxetine and norfluoxetine in frozen plasma samples for at least 185 days. Some samples in food study were stored for this period.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Geneva Pharmaceuticals on its fluoxetine hydrochloride capsules, 20 mg, lot #6496022, comparing it to the reference product Prozac® capsules 20 mg, lot #9AP49A manufactured by Dista (Lilly) has been found acceptable by the Division of Bioequivalence. The study demonstrates that Geneva'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 Geneva Pharmaceuticals on its fluoxetine hydrochloride capsules 20 mg, lot #6496022, comparing it to the reference product Prozac® capsules 20 mg, lot #9AP49A manufactured by Dista (Lilly) has been found incomplete by the Division of Bioequivalence.

3. The dissolution testing data on the test product are 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 (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.

4. The waiver of the *in vivo* bioequivalence study requirements for the firm's 10 mg capsules is denied pending approval of the 20 mg strength of the test product.

5. From the bioequivalence point of view, the firm has met the *in vitro* dissolution requirements, but not the *in vivo* bioequivalence requirements and the application is incomplete.

The firm should be informed of the deficiency #1 and the following comments:

1. Food study: Samples from subject #23 were run on two separate days; period I and II on Oct. 16, 1996 and period III samples were run on Nov. 8, 1996. Please note for future studies that all samples from one subject should be run on the same day.

2. None of the samples analyzed during the study had fluoxetine or norfluoxetine plasma concentrations higher than ng/mL. Most of the samples were between ng/mL for fluoxetine and between ng/mL for norfluoxetine. The firm has used the standard curve of 0.50-100 ng/mL and these QC sample

concentrations: low ng/mL, medium 40 ng/mL, and high ng/mL. In the future, the concentrations of the quality control samples should be chosen within and/or much closer to the concentration range of the actual plasma concentrations of the drug.

/S/

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

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 6/17/1997.

Concur: /S/ Date 6/17/97
for Nicholas Fleischer, Ph.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				
Pregelatinized Starch				
Magnesium Stearate,NF				
#3 Opaque White Cap/Opaque White body, body and cap imprinted GG 575 in green ink				
#3 Opaque White Cap/Opaque White body, body and cap imprinted GG 550 in black ink				
Total weight				

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

Table 2

Fluoxetine Plasma Concentrations (ng/mL) (n=41) Dose=2x20 mg Arithmetic Means and Standard Deviation: Fasting Study

Time (h)	Test		Reference		Test/Ref
	Mean	SD	Mean	SD	
0	0		0		
1	0.782	0.815	0.828*	0.795	0.94
2	3.805	2.499	4.198*	3.087	0.91
3	8.195	3.928	8.940*	4.729	0.92
4	12.467	5.016	13.009*	5.393	0.96
5	17.099	5.076	17.015*	5.196	1.00
6	21.130	6.474	20.062*	5.002	1.05
7	21.376	5.767	21.033*	5.615	1.02
8	21.945	6.276	20.984*	5.338	1.04
10	19.694	5.094	19.469*	5.241	1.01
12	19.690	5.670	19.687*	5.626	1.00
16	17.911	5.510	18.094*	5.857	0.99
24	14.330	4.845	14.391*	5.063	0.99
36	11.682	5.151	11.966*	4.888	0.98
48	9.087*	4.577	8.861**	4.370	1.02
60	7.775**	4.748	7.919****	4.800	0.98
72	6.235**	4.148	6.289*	3.865	0.99
96	4.479**	3.791	4.368**	3.347	1.02
120	3.235**	3.197	3.258***	3.014	0.99
144	2.429**	2.894	2.312**	2.690	1.05
168	1.997*	2.679	1.784**	2.365	1.12
336	0.452**	1.033	0.409***	0.974	1.10
504	0.108*	0.338	0.107**	0.337	1.01
672	0.015*	0.093	0.030**	0.130	0.50
Pharmacokinetic Parameters					
AUC_{0-t} (ng/mLxh)	1392.3	987.9	1340.3*	926.4	1.04
AUC_{0-inf} (ng/mLxh)	1486.5	1064	1444.4*	979	1.03
C_{max} (ng/mL)	23.593	6.080	22.610*	5.347	1.04
T_{max} (h)	7.880	2.262	8.350*	2.778	0.94
$t_{\frac{1}{2}}$ (h)	48.83	29.287	48.43*	28.012	1.01
Elim. rate constant (h^{-1})	0.01789	0.0070	0.01760*	0.0064	1.02

* n=40, ** n=39, *** n=37, **** n=36

Table 3

Fluoxetine Pharmacokinetic Parameters in Fasting Study
Least Squares Means ± Standard Error (n=41) (Dose 2x20 mg)

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (ng/mLxh)	1395.2±37	1326.8*±38	1.05	98.4-111.9%
AUC_{0-inf} (ng/mLxh)	1490.2±32	1428.0*±33	1.04	99.0-109.7%
C_{max} (ng/mL)	23.634±.36	22.543*±.38	1.05	100.9-108.8%
$LNAUC_{0-t}$	1121.25(74)@	1110.81*(66)	1.01	96.6-107.7%
$LNAUC_{0-inf}$	1190.22(75)	1191.52*(68)	0.99	96.7-105.7%
LNC_{max}	22.678(31)	21.941*(26)	1.03	99.5-108.1%

* n=40, @=% CV

For log transformed parameters, the antilog of the mean (geometric mean) is reported.

Table 4

Fluoxetine Test/Reference Ratios for Pharmacokinetic Parameters in Individual Subjects (Fasting Study)

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	1			
2	1			
3	1			
5	1			
6	2			
7	2			
10	2			
11	1			
12	2			
13	2			
14	1			
15	2			
16	1			
17	1			
19	2			
20	2			
21	1			
22	2			
23	1			
24	2			
25	1			
26	1			
27	2			
28	2			
29	1			
30	1			
31	1			
32	2			
33	1			
34	2			
35	2			
36	2			
37	1			
38	1			
39	2			
40	1			
41	2			
43	2			
44	1			
45	1			
Mean		1.04	1.02	1.04
Range				

Table 5

Fluoxetine AUC_{0-t}/AUC_{0-inf} Ratios (Fasting Study)

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1		
2		
3		
5		
6		
7		
10		
11		
12		
13		
14		
15		
16		
17		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
31		
32		
33		
34		
35		
36		
37		
38		
39		
40		
41		
42		
43		
44		
45		
Mean	0.942	0.937
Range		

Table 6

Norfluoxetine Plasma Concentrations (ng/mL) (n=41) Dose=2x20 mg): Arithmetic Means and Standard Deviation: Fasting Study

Time (h)	Test		Reference		Test/Ref
	Mean	SD	Mean	SD	
0	0.019	0.121	0.046*	0.212	0.413
1	0.069	0.225	0.056*	0.212	1.232
2	0.861	0.735	0.879*	0.628	0.979
3	2.209	1.444	2.089*	1.252	1.057
4	3.463	1.794	3.498*	1.819	0.989
5	5.080*	2.290	4.897*	2.028	1.037
6	6.471	2.666	6.400*	2.831	1.011
7	7.210	2.906	7.150*	3.117	1.008
8	8.117	3.510	7.950*	3.543	1.021
10	8.821	3.673	8.476*	3.528	1.040
12	9.690	4.118	9.589*	4.181	1.010
16	11.146	4.804	10.874*	4.186	1.025
24	10.658	4.114	10.400*	4.309	1.024
36	13.734	5.312	13.380*	5.057	1.026
48	12.844*	4.749	13.197**	4.387	0.973
60	14.889**	5.174	14.524****	5.341	1.025
72	13.692**	4.909	13.003*	4.542	1.053
96	13.336**	4.488	13.354**	4.424	0.998
120	12.930**	4.218	12.366***	4.304	1.045
144	11.773**	3.984	11.834**	4.292	0.994
168	11.483*	4.569	11.390**	4.142	1.008
336	5.845**	2.858	5.889***	3.037	0.992
504	2.820*	2.240	2.717**	2.098	1.038
672	1.193*	1.380	1.261**	1.489	0.946
Pharmacokinetic Parameters:					
AUC_{0-t} (ng/mLxh)	4540.1	1759	4403.2*	1821	1.031
AUC_{0-inf} (ng/mLxh)	4917.9**	2018	5013.4**	2115	0.980
C_{max} (ng/mL)	15.510	5.207	15.548*	5.169	0.997
T_{max} (h)	81.393	57.62	74.344*	43.13	1.094
$t_{½}$ (h)	149.72**	52.01	165.66**	69.41	0.903
Elim. rate constant (h^{-1})	0.0051**	0.001	0.0048**	0.001	1.062

* n=40, ** n=39, *** n=37, **** n=36

Table 7

Norfluoxetine Pharmacokinetic Parameters in Fasting Study Least Squares Means ± Standard Error (n=41) (Dose 2x20 mg)

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (ng/mLxh)	4542.9±51.9	4373.7*±59.4	1.04	101.0-106.7%
AUC_{0-inf} (ng/mLxh)	4944.8**±69.1	4912.5**±69.1	1.00	97.3-104.0%
C_{max} (ng/mL)	15.507±0.22	15.559*±0.23	0.99	96.2-103.1%
$LNAUC_{0-t}$	4228.56(39.8)@	3982.12*(53.6)	1.06	99.9-114.2%
$LNAUC_{0-inf}$	4550.16**(41.5)	4618.54**(42.8)	0.98	98.5-104.2%
LNC_{max}	14.6168(37.1)	14.6488*(37.5)	0.99	96.6-102.6%

For log transformed parameters, the antilog of the mean (geometric mean) is reported.

* n=40, ** n=39, @ %CV

Table 8

Norfluoxetine Test/Reference Ratios for Pharmacokinetic Parameters in Individual Subjects (Fasting Study)

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	2			
2	2			
3	2			
5	2			
6	1			
7	1			
10	1			
11	2			
12	1			
13	1			
14	2			
15	1			
16	2			
17	2			
19	1			
20	1			
21	2			
22	1			
23	2			
24	1			
25	2			
26	2			
27	1			
28	1			
29	2			
30	2			
31	2			
32	1			
33	2			
34	1			
35	1			
36	1			
37	2			
38	2			
39	1			
40	2			
41	1			
43	1			
44	2			
45	2			
Mean		1.12	1.02	1.00
Range				

Table 9

Norfluoxetine AUC_{0-t}/AUC_{0-inf} Ratios (Fasting Study)

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1		
2		
3		
5		
6		
7		
10		
11		
12		
13		
14		
15		
16		
17		
19		
20		
21		
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30		
31		
32		
33		
34		
35		
36		
37		
38		
39		
40		
41		
42		
43		
44		
45		
Mean	0.933	0.912
Range		

Table 10

Fluoxetine Plasma Concentrations and Pharmacokinetic Parameters (arithmetic means ± SD) In Food Study (ng/mL) (Dose=2x20 mg) (n=19)

Time h	Test-fasted A	Test-fed B	Ref-fed C	A/B	A/C	B/C
0	0	0	0			
1	1.114±0.85	0.255±0.46	0.039±0.17	4.37	28.5	6.54
2	5.398±2.27	2.935±3.58	1.230±1.61	1.84	4.38	2.38
3	11.059±4.07	5.310±4.43	4.538±3.97	2.08	2.43	1.17
4	14.88±3.75	8.293±4.89	8.149±5.28	1.79	1.82	1.02
5	19.018±4.82	13.755±6.28	14.338±6.05	1.38	1.32	1.00
6	21.675±5.27	19.315±6.64	19.266±6.57	1.12	1.12	1.00
8	20.444±5.38	19.969±6.17	20.691±6.51	1.02	0.99	0.96
10	19.201±5.91	18.215±5.37	18.867±5.26	1.05	1.02	0.96
12	18.873±5.41	18.306±5.47	18.347±5.01	1.03	1.03	0.99
16	16.651±4.70	16.716±4.26	16.848±5.29	0.99	0.99	0.99
24	13.242±4.49	13.065±3.89	13.399±4.06	1.01	0.99	0.97
36	10.361±3.60	9.933±4.23	10.791±3.86	1.04	0.96	0.92
48	8.618±3.338	8.603±3.42	8.697±3.69	1.00	0.99	0.99
60	6.804±2.99	6.769±3.18	6.906±2.99	1.00	0.98	0.98
72	5.563±2.77	5.601±2.89	5.710±2.86	0.99	0.97	0.98
96	3.534±2.18	3.892±2.79	4.047±2.65	0.91	0.87	0.96
120	2.558±1.81	2.925±2.53	2.880±2.37	0.87	1.01	0.89
144	1.659±1.41	2.037±2.26	1.967±2.15	0.81	0.84	1.03
168	1.119±1.20	1.493±2.12	1.445±2.11	0.75	0.77	1.03
336	0.062±0.27	0.333±1.18	0.262±0.96	0.18	0.24	1.27
504	0.0	0.136±0.56	0.125±0.56	0	0	1.09
672	0.0	0.100±0.41	0.079±0.35	0	0	1.26
Parameters:						
AUC_{0-t} (ng/mLxh)	1084±457	1181.5±843	1193.2±773	0.92	0.91	0.99
AUC_{0-inf} (ng/mLxh)	1158±511	1281.3±953	1283.5±867	0.90	0.90	0.99
C_{max} (ng/mL)	22.907±5.74	21.078±6.15	21.593±6.31	1.08	1.06	0.97
T_{max} (h)	6.737±2.18	7.579±1.95	8.476±2.52	0.88	0.79	0.89
Half-life (h)	40.79±14.40	50.11±39.0	47.80±36.76	0.81	0.85	1.05
Elim. Rate constant (h^{-1})	0.0185±.005	0.0175±.006	0.0179±.005	1.05	1.03	0.97

Test-fasted and test-fed: n=19; reference-fed: n=21

Table 11

Norfluoxetine Plasma Concentrations & Pharmacokinetic Parameters (arithmetic means ± SD) in Food Study (ng/mL) (Dose=2x20 mg) (n=19)

Time h	Test-fasted A	Test-fed B	Ref-fed C	A/B	A/C	B/C
0	0	0	0			
1	0.028±0.12	0.00	0.00			
2	1.245±0.65	0.464±0.88	0.175±0.38	2.68	7.11	2.65
3	2.992±1.35	1.052±1.14	0.907±1.14	2.84	3.29	1.16
4	4.283±1.73	2.114±1.44	2.001±1.51	2.02	2.14	1.05
5	5.868±2.30	3.927±2.16	3.780±1.65	1.49	1.55	1.04
6	7.375±2.40	5.698±2.58	5.730±2.38	1.29	1.28	0.99
8	8.372±2.85	6.927±3.00	6.895±2.79	1.21	1.21	1.00
10	9.431±3.08	7.584±2.99	8.031±3.33	1.24	1.17	0.94
12	10.36±3.52	8.283±3.48	8.86±3.26	1.25	1.17	0.93
16	10.78±3.59	9.204±4.11	9.241±3.70	1.17	1.16	0.99
24	10.36±3.57	9.045±3.84	9.415±4.10	1.14	1.10	0.96
36	13.68±4.59	11.27±4.88	12.75±5.49	1.21	1.07	0.88
48	13.67±4.04	11.81±5.33	11.96±4.28	1.16	1.14	0.99
60	14.78±4.85	13.46±5.50	13.64±5.08	1.09	1.08	0.99
72	13.95±3.97	12.02±4.24	12.61±4.52	1.16	1.10	0.95
96	13.10±4.33	11.13±3.98	12.43±4.47	1.17	1.05	0.89
120	12.62±3.55	11.85±4.31	11.96±4.23	1.06	1.05	0.99
144	11.63±3.08	10.48±3.88	10.48±3.70	1.11	1.11	1.00
168	11.11±3.19	9.99±3.88	10.30±3.92	1.11	1.08	0.97
336	5.166±2.40	4.604±2.27	4.796±2.03	1.12	1.08	0.96
504	1.936±1.58	2.099±1.42	1.939±1.28	0.92	0.99	1.08
672	0.893±0.95	0.795±0.64	0.635±0.72	1.12	1.41	1.25
Parameter						
AUC_{0-t} (ng/mLxh)	4229.7±1426	3677.2±1491	3833±1340	1.15	1.10	0.96
AUC_{0-inf} (ng/mLxh)	4525±1574	4071±1469	4095.8±1471	1.11	1.10	0.99
C_{max} (ng/mL)	15.825±4.74	14.047±5.21	14.935±5.53	1.12	1.06	0.94
T_{max} (h)	79.6±33.73	79.606±27.49	77.714±38.99	0.99	1.02	1.02
Half-life (h)	139.70±38.7	154.85±64.71	143.77±56.43	0.90	0.97	1.07
Elim. rate constant (h^{-1})	0.0053±.0014	0.0049±.0014	0.0053±.0015	1.08	1.00	0.92

Test-fasted and test-fed: n=19; reference-fed: n=21

Table 12. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 and 20 mg
ANDA No.: 75049
Firm: Geneva Pharmaceuticals
Submission Date: December 31, 1996
File Name: 75049SDW.D96

I. Conditions for Dissolution Testing: FDA 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 (Dista-Lilly)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 6496034 Strength(mg) 10			Reference Product Lot # 9AL24A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	90		3.6	85		4.4
20	93		2.4	88		6.1
30	93		3.0	82		4.4
40	94		3.0	84		4.4

Sampling Times (Minutes)	Test Product Lot # 6496022 Strength(mg) 20			Reference Product Lot # 9AP49A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	95		1.5	93		2.9
20	96		1.5	92		2.9
30	97		1.3	93		4.2
40	97		1.9	94		3.6

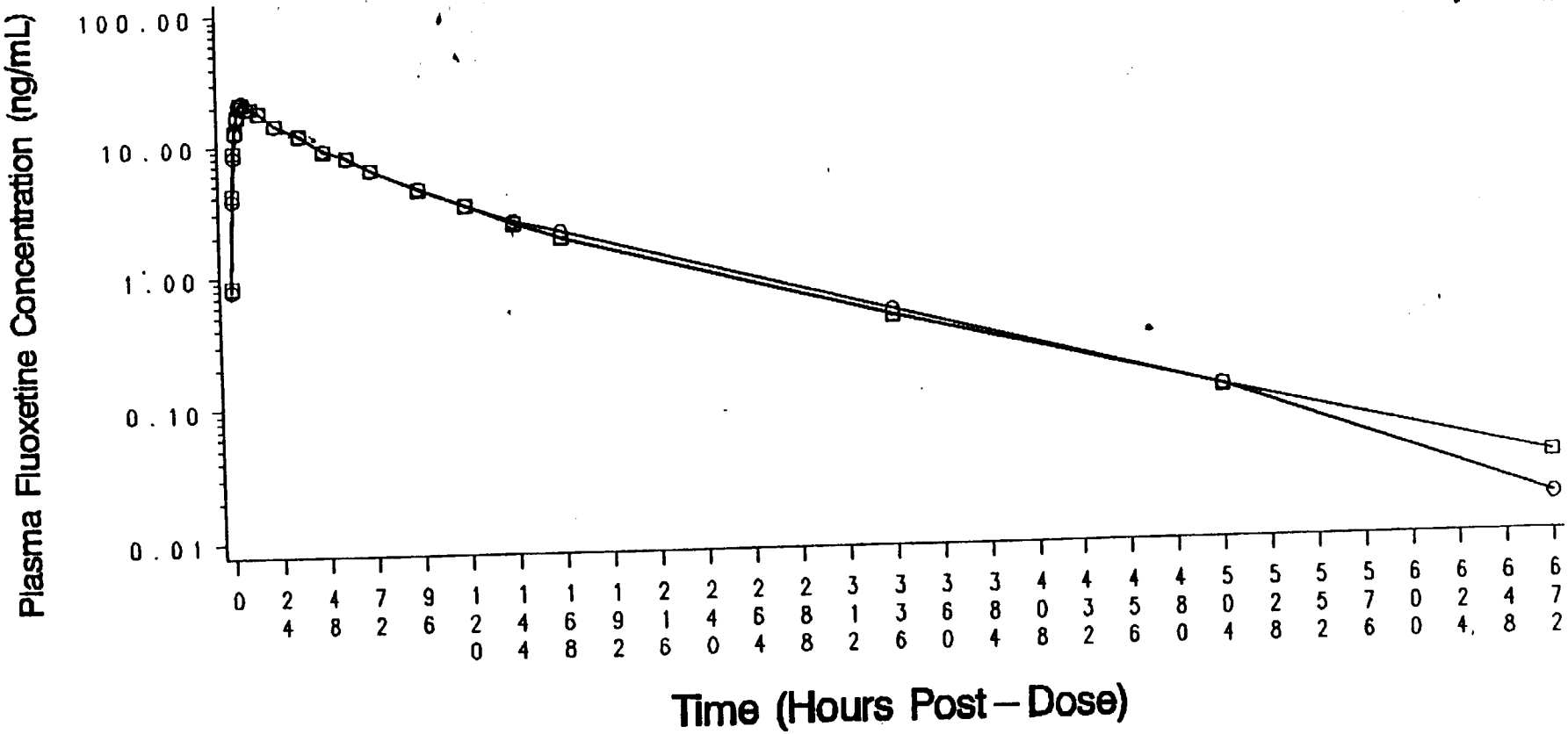
Figure 1

Fasting Study

Project No. 960380

Mean Plasma Fluoxetine Concentrations

(Semi–Log Plot)



DEFAULT (13NOV96)

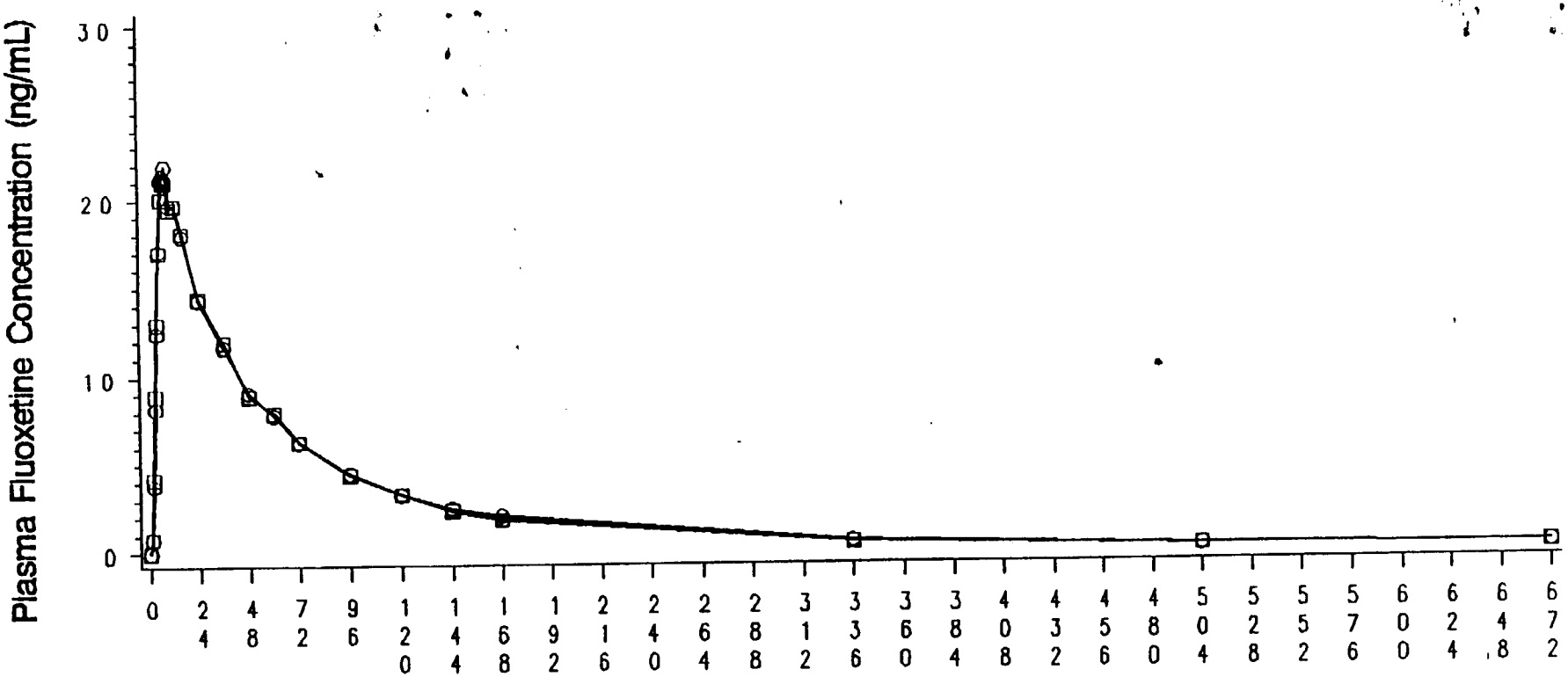
Figure 2

Project No. 960380

Mean Plasma Fluoxetine Concentrations

(Linear Plot)

Fasting Study



DEFAULT (13NOV96)

Figure 3

Project No. 960380

Mean Plasma Norfluoxetine Concentrations

(Semi – Log Plot)

Fasting Study

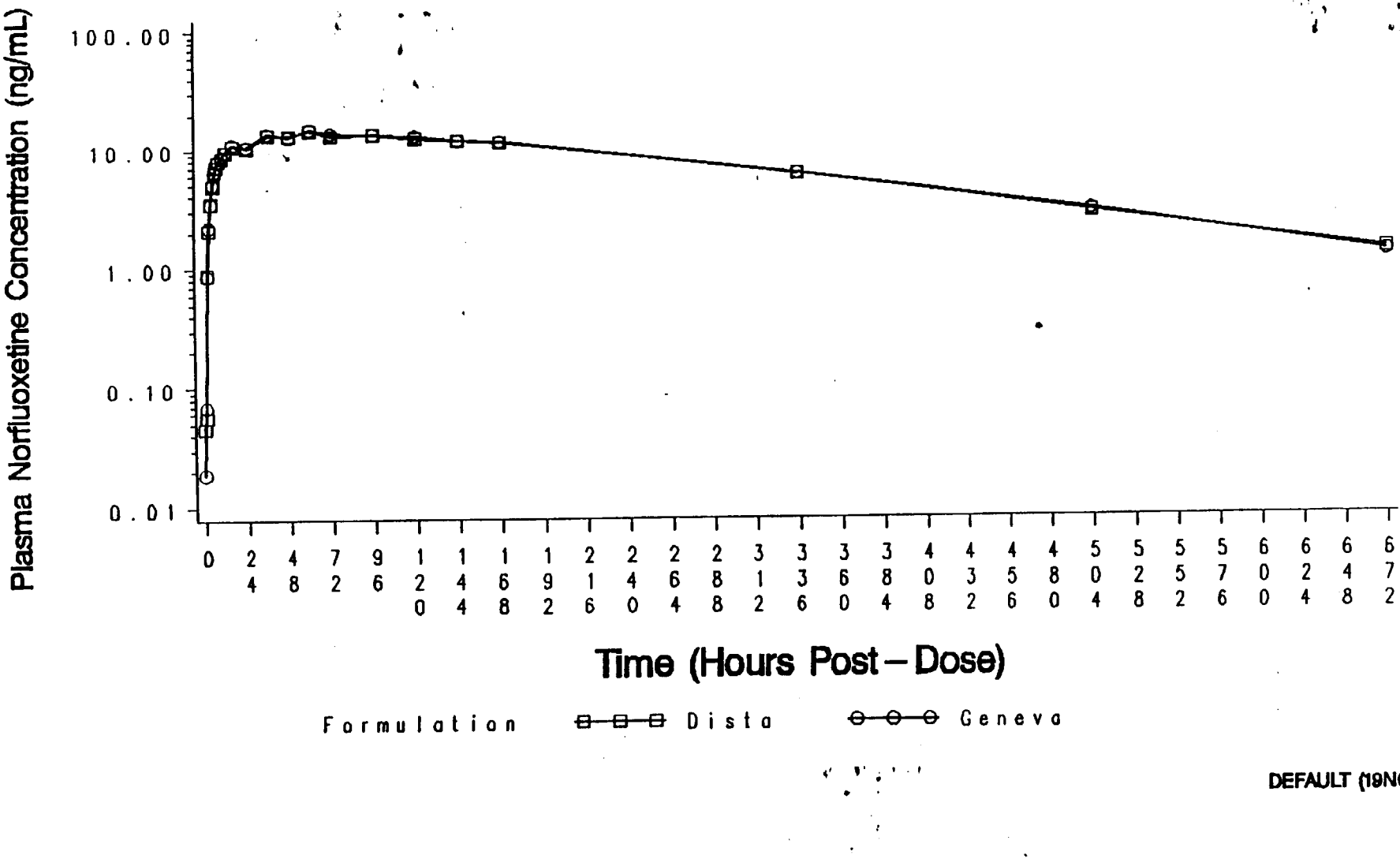


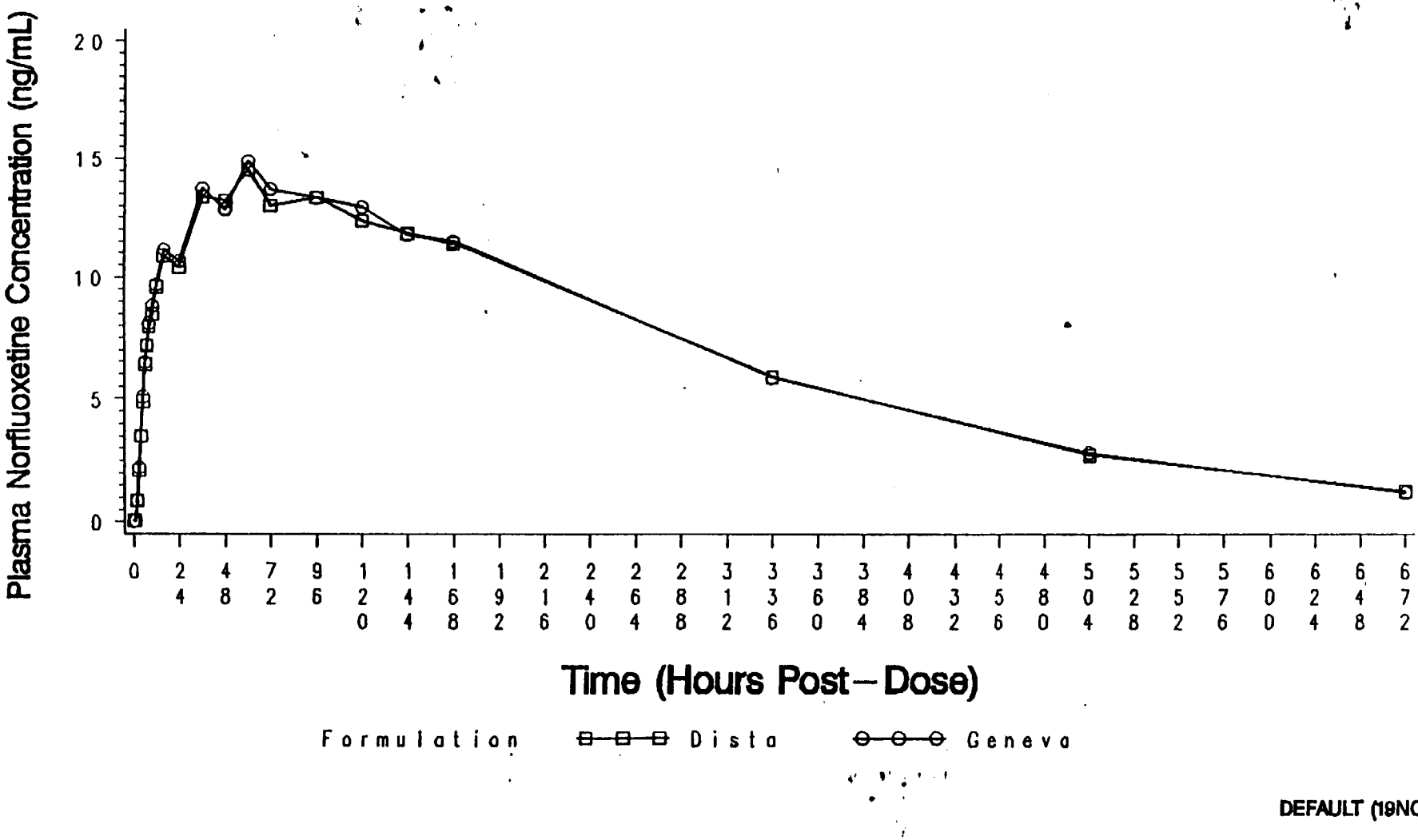
Figure 4

Project No. 960380

Mean Plasma Norfluoxetine Concentrations

(Linear Plot)

Fasting Study



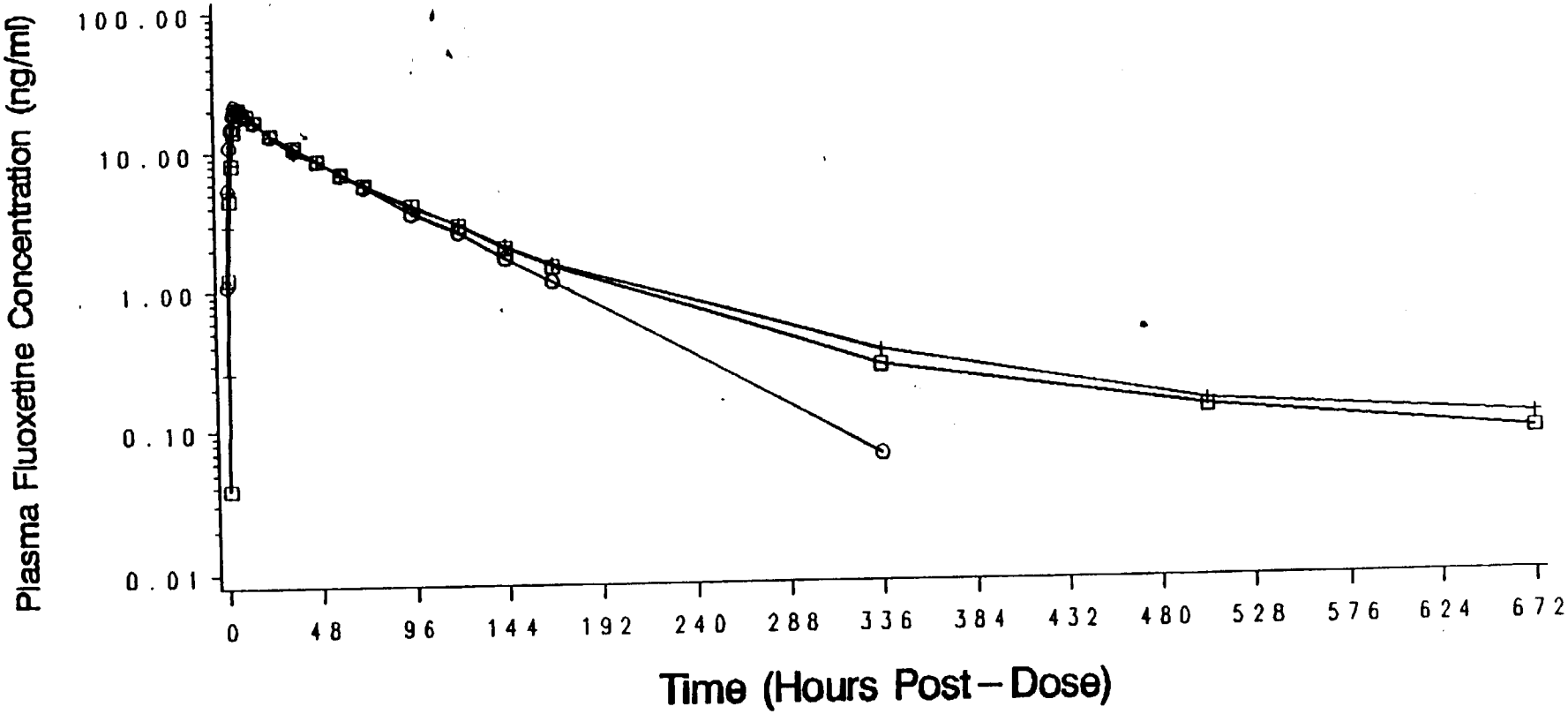
DEFAULT (19NOV98)

Figure 15

Project No. 960379

Mean Plasma Fluoxetine Concentrations

(Semi–Log Plot)



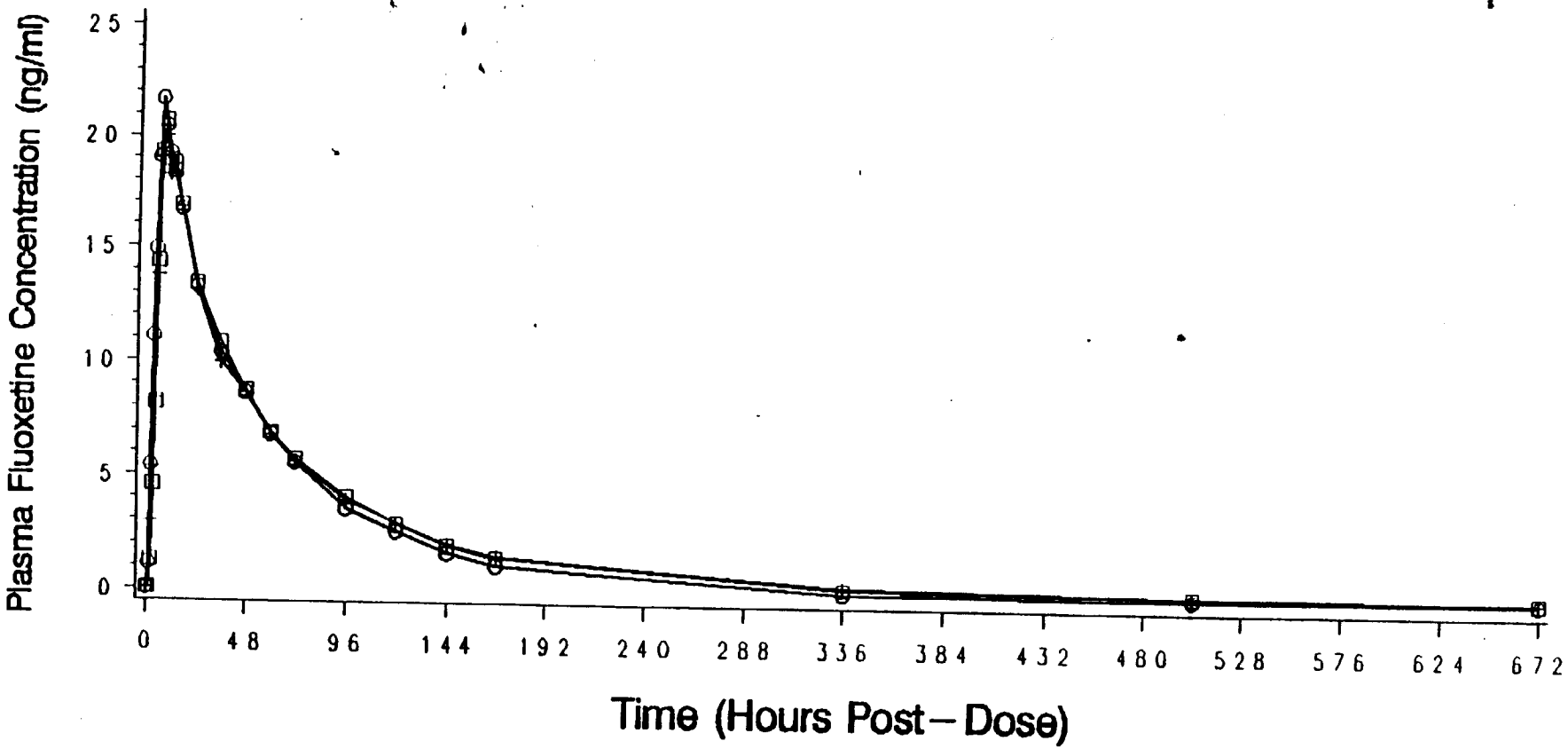
DEFAULT (26NOV96)

Figure 2 6

Project No. 960379

Mean Plasma Fluoxetine Concentrations

(Linear Plot)



DEFAULT (26NOV96)

Figure 3.7

Project No. 960379

Mean Plasma Norfluoxetine Concentrations

(Semi – Log Plot)

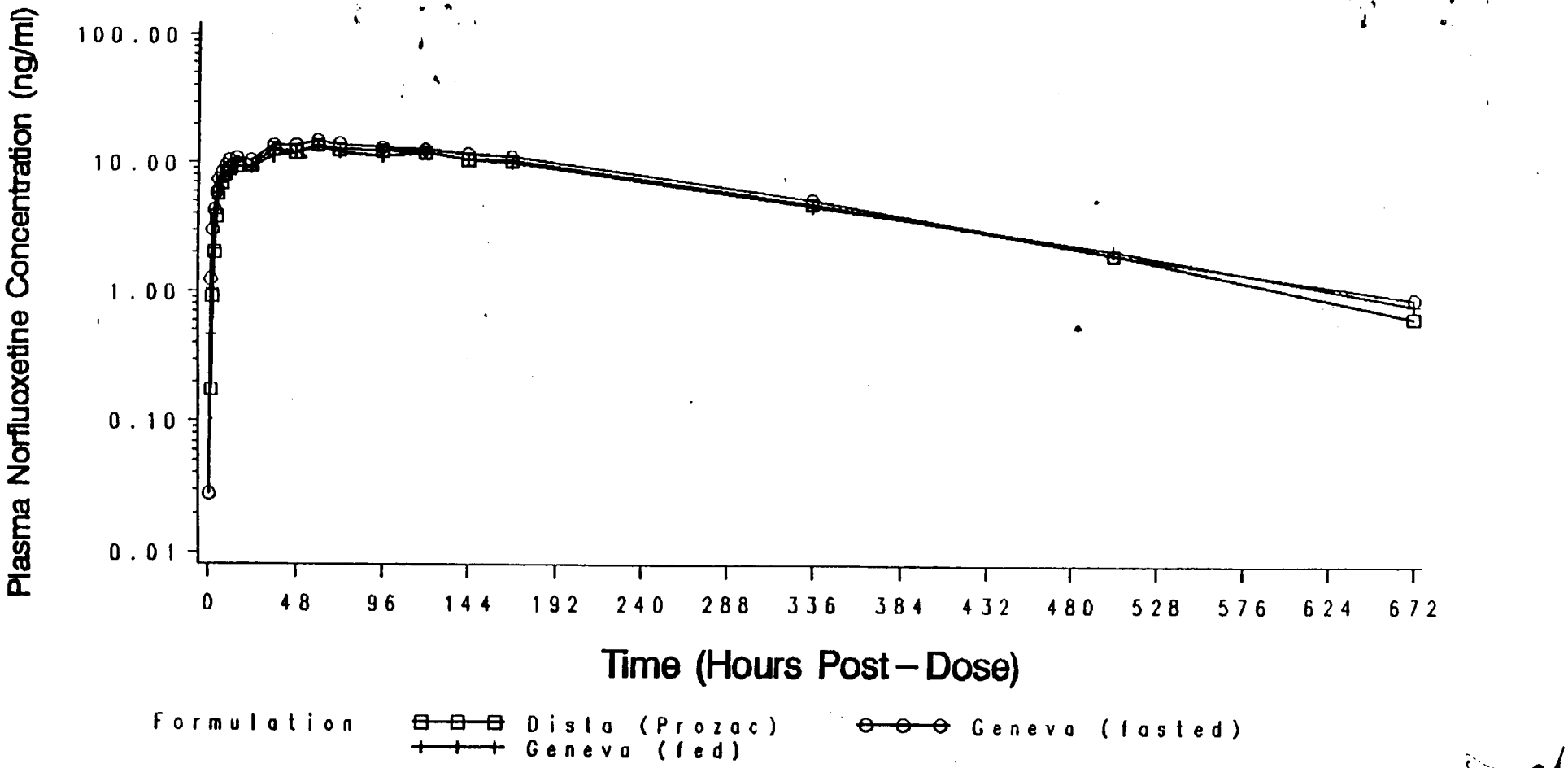


Figure 8

Project No. 960379

Mean Plasma Norfluoxetine Concentrations

(Linear Plot)

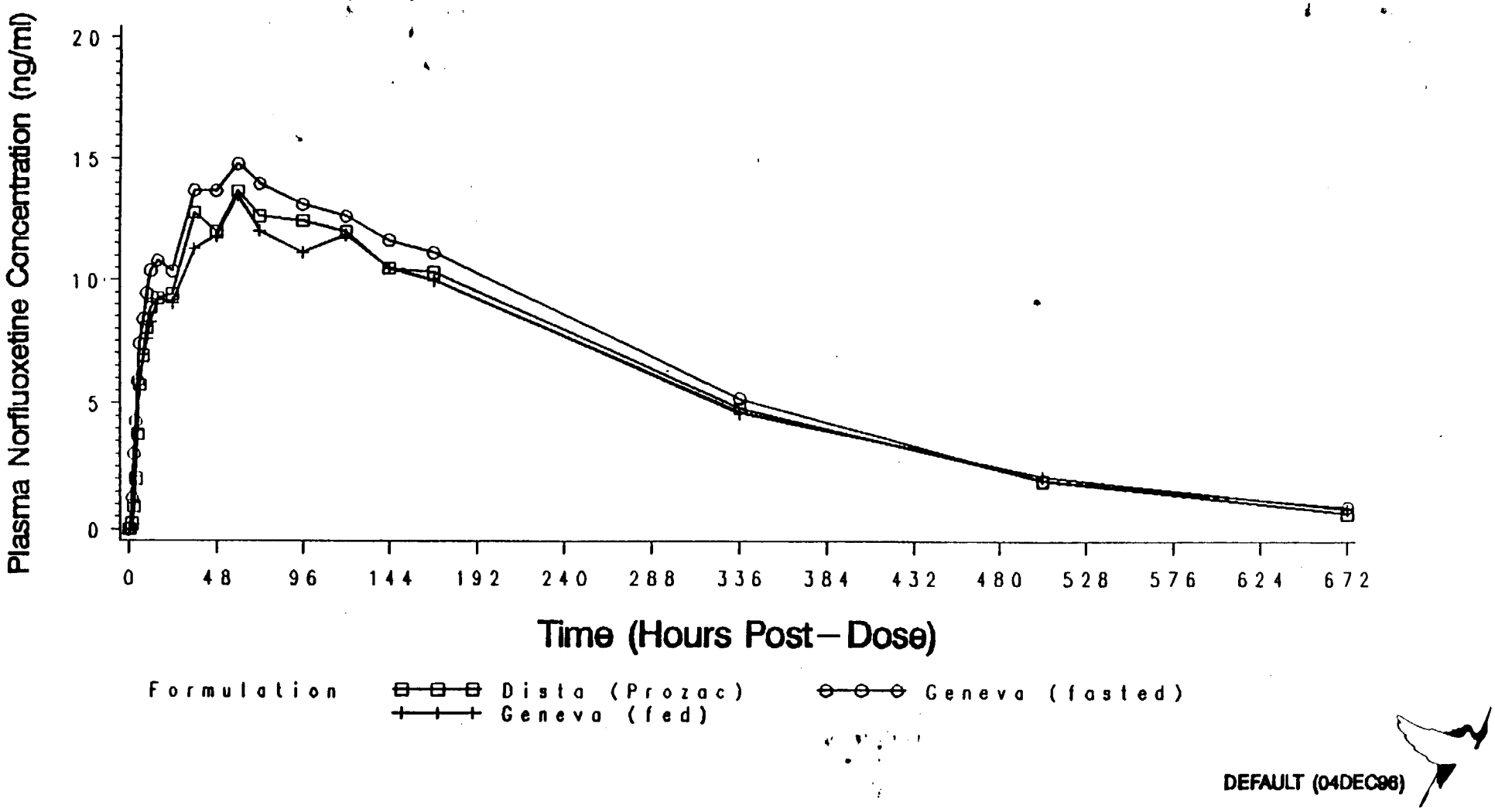


TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Fasting Study

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
A	1	1	168					Did not show for blood draw
A	2	1	48	0	1	35	Late	Subject arrived late
A	2	1	144	0	0	33	Late	Subject arrived late
A	2	1	504	0	0	16	Late	Subject arrived late
A	3	1	10	0	0	4	Late	Due to preceding blood draw
A	6	2	60	0	5	5	Late	Subject arrived late
A	6	2	336	0	1	7	Late	Subject arrived late
A	6	2	504	0	0	23	Late	Subject arrived late
A	6	2	672	0	1	46	Late	Subject arrived late
A	7	2	120	0	2	2	Late	Subject arrived late
A	7	2	144					Did not show for blood draw
A	7	2	168	0	3	52	Late	Subject arrived late
A	7	2	336	0	2	44	Late	Subject arrived late
A	7	2	504	0	0	15	Late	Subject arrived late
A	8	1	48	0	0	7	Late	Subject arrived late
A	8	1	72	0	2	26	Late	Subject arrived late
A	8	1	96	0	1	53	Late	Subject arrived late
A	8	1	120	0	1	3	Late	Subject arrived late
A	8	1	144	0	2	4	Late	Subject arrived late
A	8	1	168	0	1	45	Late	Subject arrived late
A	8	1	504	0	3	29	Late	Subject arrived late
A	8	1	672	0	2	0	Late	Subject arrived late
A	9	1	24	0	0	5	Late	Subject arrived late

A = Geneva 2 x 20 mg fluoxetine HCl capsules
B = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules

File DEVSS.OUT created 08/NOV/96 03:49pm by WESSER01. DataEase Ver# 4.53, Internal Ver# 94.01-F05-R05

TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Fasting Study

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
A	10	2	672	0	0	6	Late	Subject arrived late
A	12	2	48	0	0	7	Late	Subject arrived late
A	13	2	16	0	0	11	Late	Subject arrived late Subject was sleeping.
A	13	2	120					Sample taken. Blood tubes mislabeled.
A	13	2	672	0	1	6	Late	Subject arrived late
A	14	1	96	0	0	19	Early	Due to previous commitment Subject had to go to work.
A	15	2	72	0	0	6	Late	Subject arrived late
A	15	2	144	0	0	8	Late	Subject arrived late
A	15	2	168	0	2	11	Late	Subject arrived late
A	15	2	336	0	0	8	Late	Subject arrived late.
A	15	2	504	0	0	8	Late	Subject arrived late
A	17	1	2	0	0	5	Late	Subject arrived late
A	17	1	60					Did not show for blood draw
A	17	1	72					Did not show for blood draw
A	18	1	120	0	0	3	Late	Subject arrived late
A	18	1	672	2	9	8	Late	Subject arrived late Permission given for late blood draw.
A	19	2	60	0	2	54	Late	Subject arrived late
A	19	2	72	0	14	54	Late	Subject arrived late
A	19	2	96					Did not show for blood draw

A = Geneva 2 x 20 mg fluoxetine HCl capsules
B = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules

File DEVSS.OUT created 08/NOV/96 03:49pm by WESSER01. DataEase Ver# 4.53, Internal Ver# 94.01-F05-R05

TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Fasting Study

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
A	19	2	168	0	1	42	Late	Subject arrived late
A	19	2	336					Did not show for blood draw
A	19	2	504	0	1	3	Late	Subject arrived late
A	19	2	672	0	1	33	Late	Subject arrived late
A	21	1	60	0	0	23	Late	Subject arrived late
A	21	1	120	0	0	11	Late	Subject arrived late
A	21	1	504					Did not show for blood draw
A	21	1	672	0	0	3	Late	Subject arrived late
A	22	2	120	0	0	18	Late	Subject arrived late
A	25	1	96	0	0	6	Late	Difficulty with veins
A	27	2	48					Did not show for blood draw
A	27	2	60					Sample not obtained
A	27	2	72					Did not show for blood draw
A	27	2	96					Did not show for blood draw
A	27	2	120					Did not show for blood draw
A	27	2	144					Did not show for blood draw
A	27	2	336					Did not show for blood draw
A	29	1	672	2	11	29	Late	Subject arrived late Permission given for late draw.
A	33	1	504	0	1	4	Late	Subject arrived late
A	35	2	168	0	0	10	Late	Subject arrived late
A	35	2	504	0	0	28	Late	Subject arrived late
A	40	1	60	0	0	26	Late	Subject arrived late

A = Geneva 2 x 20 mg fluoxetine HCl capsules
B = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules

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TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Fasting Study

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
A	41	2	144	0	0	14	Late	Subject arrived late
A	41	2	672					Did not show for blood draw
A	42	2	144	0	0	11	Late	Subject arrived late
A	42	2	504	0	2	4	Late	Subject arrived late
A	44	1	336	2	7	26	Late	Subject arrived late
A	44	1	504	0	17	9	Early	Reason was not recorded
A	44	1	672	1	22	1	Early	Reason was not recorded
A	45	1	10	0	0	5	Late	Difficulty with veins
B	1	2	120					Sample time not recorded
B	2	2	48					Did not show for blood draw
B	2	2	60					Did not show for blood draw
B	2	2	96					Did not show for blood draw
B	2	2	120					Sample time not recorded
B	2	2	144					Did not show for blood draw
B	2	2	168					Did not show for blood draw
B	2	2	336					Did not show for blood draw
B	2	2	504					Did not show for blood draw
B	2	2	672	0	3	36	Late	Subject arrived late
B	3	2	144	0	0	3	Late	Subject arrived late
B	3	2	336	0	2	31	Late	Subject arrived late
B	4	1	6	0	0	3	Late	Subject arrived late
B	5	2	144	0	0	9	Late	Subject arrived late

A = Geneva 2 x 20 mg fluoxetine HCl capsules
B = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules

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TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE Fasting Study

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Deviation Hrs	Deviation Min	Deviation Late/Early	Reason/Comment
B	5	2	336					Did not show for blood draw
B	6	1	6	0	0	4	Late	Difficulty with veins
B	6	1	48	0	0	37	Late	Subject arrived late
B	6	1	672	0	0	12	Late	Subject arrived late
B	7	1	72	0	2	26	Late	Subject arrived late
B	7	1	96	0	1	47	Late	Subject arrived late
B	7	1	120	0	1	2	Late	Subject arrived late
B	7	1	144	0	2	4	Late	Subject arrived late
B	7	1	168	0	1	45	Late	Subject arrived late
B	7	1	504	0	2	27	Late	Subject arrived late
B	12	1	36	0	0	4	Late	Difficulty with veins
B	12	1	672	0	0	4	Late	Subject arrived late
B	13	1	336	0	0	51	Late	Subject arrived late
B	14	2	120					Sample taken. Blood tubes mislabeled.
B	14	2	672	0	0	30	Late	Subject arrived late
B	17	2	60					Did not show for blood draw
B	17	2	96	0	12	0	Late	Subject arrived late
B	17	2	672	0	0	5	Late	Subject arrived late
B	19	1	48	0	0	37	Late	Subject arrived late
B	19	1	96	0	0	31	Late	Subject arrived late
B	19	1	120	0	0	40	Late	Subject arrived late
B	19	1	168	0	0	47	Late	Subject arrived late

A = Geneva 2 x 20 mg fluoxetine HCl capsules
B = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules

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TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Fasting Study

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
B	19	1	336	0	0	59	Late	Subject arrived late
B	19	1	504	0	0	50	Late	Subject arrived late
B	19	1	672	0	0	42	Late	Subject arrived late
B	21	2	336					Did not show for blood draw
B	21	2	504	0	0	27	Late	Subject arrived late
B	21	2	672	0	0	23	Late	Subject arrived late
B	22	1	96	0	0	15	Late	Subject arrived late
B	22	1	336	0	0	28	Late	Subject arrived late
B	23	2	672					Sample taken. Blood tube mislabeled.
B	25	2	6					Sample time not recorded
B	26	2	5	0	0	3	Late	Difficulty with veins
B	26	2	48	0	0	12	Late	Subject arrived late
B	26	2	60					Did not show for blood draw
B	26	2	120	0	0	5	Late	Subject arrived late
B	27	1	24	0	0	18	Late	Blood drawn a second time. The first tube of blood broke in the centrifuge.
B	29	2	48	0	0	8	Late	Subject arrived late
B	31	2	120					Sample time not recorded
B	32	1	10	0	0	3	Late	Difficulty with veins
B	32	1	16	0	0	6	Late	Difficulty with veins
B	33	2	16	0	0	4	Late	Difficulty with veins
B	33	2	672	0	3	3	Late	Subject arrived late

A = Geneva 2 x 20 mg fluoxetine HCl capsules
B = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules

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TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Fasting Study

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
B	34	1	96	0	0	3	Late	Due to preceding blood draw
B	35	1	672	0	0	19	Late	Subject arrived late
B	37	2	60	0	2	33	Late	Subject arrived late
B	38	2	60					Did not show for blood draw
B	38	2	120	0	0	13	Late	Subject arrived late
B	38	2	144	0	0	39	Late	Subject arrived late
B	38	2	672	0	0	12	Late	Subject arrived late
B	40	2	60	0	0	18	Late	Subject arrived late
B	40	2	144	0	0	6	Late	Subject arrived late
B	40	2	168	0	0	5	Late	Subject arrived late
B	42	1	48	0	1	22	Late	Subject arrived late
B	43	1	144	0	0	3	Late	Subject arrived late
B	44	2	4	0	0	3	Late	Difficulty with veins
B	44	2	5	0	0	3	Late	Difficulty with veins
B	44	2	120	0	0	9	Late	Subject arrived late
B	44	2	336	0	19	35	Early	Due to previous commitment Drawn one day early.
B	44	2	672	0	17	4	Early	Due to previous commitment
B	46	1	5					Sample time not recorded
B	46	1	168	0	0	4	Late	Subject arrived late
B	46	1	672	0	0	29	Late	Subject arrived late

A = Geneva 2 x 20 mg fluoxetine HCl capsules
B = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules

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Food-Study

APPENDIX 1

Contraventions To The Protocol During Sample Collection

Period	Subject No.	Contravention	Time of Contravention (Post-Dose)
1	1	1 cup of coffee	between 36- and 48-hour blood draws
	2	1 12 oz. can of Dr. Pepper	between 144- and 168-hour blood draws
	2	6 beers, 5 sodas	between 168- and 336-hour blood draws
	2	6 beers, 9 cups coffee	between 336- and 504-hour blood draws
	3	2 cups of coffee, 1 soda	between 48-and 60-hour blood draws
	3	not recorded	between 168- and 336-hour blood draws
	3	not recorded	between 504- and 672-hour blood draws
	4	3 12 oz. beers, ½ liter a day of Diet Pepsi	between 336- and 504-hour blood draws
	5	not recorded	between 336- and 504-hour blood draws
	6	not recorded	between 504- and 672-hour blood draws
	7	1 Kit Kat chocolate bar	between 168- and 336-hour blood draws
	7	3 chocolate chip cookies	between 336- and 504-hour blood draws
	8	3 12 oz. beers, 3 12 oz. Pepsi	between 336- and 504-hour blood draws
	10	3 cups of ice tea, Hershey chocolate bar, Mountain Dew	between 336- and 504-hour blood draws
	10	2 Mountain Dews, 12 chocolate donuts	between 504- and 672-hour blood draws
	12	not recorded	between 168- and 336-hour blood draws
	12	not recorded	between 336- and 504-hour blood draws
	13	5 Cokes	between 168- and 336-hour blood draws

Food-Study

Period -	Subject No.	Contravention	Time of Contravention (Post-Dose)
	13	12 beers, 5 12 oz. cans of Coke	between 336- and 504-hour blood draws
	14	coffee	between 168- and 336-hour blood draws
	15	3 beers, 3 gins, 3 cups coffee, 3 Cokes	between 168- and 336-hour blood draws
	15	4 12 oz. beers, 7 cups of coffee, 4 12 oz. Cokes	between 336- and 504-hour blood draws
	16	3-4 cups coffee	between 168- and 336-hour blood draws
	16	5 12 oz. cans of Mountain Dew	between 336- and 504-hour blood draws
	18	6 Cokes, 1 Snickers chocolate bar	between 168- and 336-hour blood draws
	18	12 beers, 6 12 oz. cans of Coke	between 336- and 504-hour blood draws
	19	1 liter of Pepsi, 6 chocolate donuts	between 336- and 504-hour blod draws
	21	4 beers	between 168- and 336-hour blood draws
	22	6 beers, 12 pack Mountain Dew	between 168- and 336-hour blood draws
	22	12 cans of Mountain Dew	between 336-hour and 504-hour blood draws
	23	12 beers, 12 pack Mountain Dew	between 168- and 336-hour blood draws
	23	24 12 oz. cans of beer, 8 12 oz. cans of Mountain Dew	between 336- and 504-hour blood draws
2	1	3 oz. Of Pepsi	between 48- and 60-hour blood draws
	2	3-4 chocolate custard filled donuts	between 60- and 72-hour blood draws
	6	not recorded	between 336- and 504 hour blood draws
	6	not recorded	between 504- and 672-hour blood draws
	7	1 chocolate chip cookie	between 48- and 60-hour blood draws
	10	12 oz. of ice tea	between 72- and 96-hour blood draws

Food - Study

Period	Subject No.	Contravention	Time of Contravention (Post-Dose)
	11	not recorded	between 336- and 504-hour blood draws
	11	not recorded	between 504- and 672-hour blood draws
	13	1 ice cream sandwich	between 48- and 60-hour blood draws
	14	3 oz. of Coke, alcohol consumption was not recorded	between 72- and 96-hour blood draws
	14	not recorded	between 504- and 672-hour blood draws
	15	1 12 oz. can of Coke	between 168- and 336-hour blood draws
	17	not recorded	between 36- and 48-hour blood draw
	18	not recorded	between 504- and 672-hour blood draws
	22	not recorded	between 144- and 168-hour blood draws
3	5	not recorded	between 72- and 96-hour blood draws
	7	not recorded	betweeb 36- and 48-hour draws
	8	12 oz. of Pepsi	approx. 318 hours
	13	1 12 oz. can of beer	between 120- and 144-hour blood draws
	18	not recorded	between 36- and 48-hour draws
	18	12 oz. Of Coke	approx. 327 hours

Revised by Gwenn Stever. on 14/NOV/96.

Food-Study

TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Regimen	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
A	3	1	336					Did not show for blood draw
A	3	1	504	2	9	27	Late	Reason was not recorded
A	3	1	672					Did not show for blood draw
A	5	1	504					Did not show for blood draw
A	6	1	48	0	0	40	Late	Subject arrived late
A	6	1	120	0	0	3	Late	Subject arrived late
A	6	1	672					Did not show for blood draw
A	9	1	60	0	0	30	Late	Subject arrived late
A	9	1	120	0	0	15	Late	Subject arrived late
A	9	1	168	0	0	3	Late	Difficulty with veins
A	9	1	504	0	0	6	Late	Subject arrived late
A	9	1	672	0	0	13	Late	Subject arrived late
A	11	1	2	0	0	3	Late	Difficulty with veins
A	11	1	5	0	0	3	Late	Difficulty with veins
A	11	1	48	0	0	27	Late	Subject arrived late
A	11	1	72	0	0	42	Late	Subject arrived late
A	11	1	120	0	0	3	Late	Subject arrived late
A	12	2	24	0	0	4	Late	Difficulty with veins
A	12	2	96	0	0	14	Late	Subject arrived late
A	14	2	672					Did not show for blood draw
A	18	1	48	0	0	4	Late	Due to preceding blood draw
A	20	2	48	0	0	5	Late	Due to preceding blood draw

A = Geneva 2 x 20 mg fluoxetine HCl capsules (fasted)
B = Geneva 2 x 20 mg fluoxetine HCl capsules (fed)
C = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules (fed)

File DEVSS.OUT created 14/NOV/96 12:42pm by STEVEG01. DataBase Ver# 4.53, Internal Ver# 94.01-F05-R05

Food - study

TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Regimen	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Late/ Early	Reason/Comment
B	1	1	336	3	9	56	Late	Reason was not recorded
B	5	3	48	0	0	5	Late	Subject arrived late
B	5	3	96					Did not show for blood draw
B	5	3	168	0	0	16	Late	Subject arrived late
B	6	2	48	0	0	12	Late	Subject arrived late
B	6	2	72	0	0	3	Late	Subject arrived late
B	6	2	120	0	0	6	Late	Subject arrived late
B	6	2	504					Did not show for blood draw
B	6	2	672					Did not show for blood draw
B	8	1	120	0	0	6	Late	Subject arrived late
B	8	1	504	0	0	3	Late	Subject arrived late
B	9	3	96	0	0	24	Late	Subject arrived late
B	9	3	120	0	0	5	Late	Subject arrived late
B	9	3	144	0	0	4	Late	Subject arrived late
B	9	3	504	0	0	10	Late	Subject arrived late
B	9	3	672	0	0	22	Late	Subject arrived late
B	12	1	336					Did not show for blood draw
B	12	1	504					Did not show for blood draw
B	17	2	2	0	0	7	Late	Difficulty with veins
B	17	2	4	0	0	4	Late	Due to preceding blood draw
B	17	2	16					Sample not obtained Difficulty with veins
B	17	2	48					Did not show for blood draw

A = Geneva 2 x 20 mg fluoxetine HCl capsules (fasted)
B = Geneva 2 x 20 mg fluoxetine HCl capsules (fed)
C = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules (fed)

Food - study

TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Regimen	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Deviation Hrs	Deviation Min	Late/ Early	Reason/Comment
B	17	2	72	0	0	17	Late	Subject arrived late
B	17	2	96	0	0	28	Late	Subject arrived late
B	17	2	336	0	0	5	Late	Subject arrived late
B	18	2	48	0	0	3	Late	Due to preceding blood draw
B	18	2	672					Did not show for blood draw
B	19	2	48	0	0	5	Late	Due to preceding blood draw
B	22	2	48	0	0	3	Late	Due to preceding blood draw
B	22	2	96	0	0	3	Late	Subject arrived late
B	22	2	168	0	0	5	Late	Subject arrived late
B	22	2	672	0	0	59	Late	Subject arrived late
B	23	3	144	0	0	8	Late	Subject arrived late
C	2	2	168	0	0	5	Late	Subject arrived late
C	2	2	336	0	1	35	Late	Subject arrived late
C	6	3	48	0	0	8	Late	Subject arrived late
C	6	3	120	0	0	20	Late	Subject arrived late
C	7	3	48					Did not show for blood draw
C	7	3	168	0	0	28	Late	Subject arrived late
C	7	3	336	0	0	13	Late	Subject arrived late
C	7	3	672	0	0	4	Late	Subject arrived late
C	8	2	2	0	0	4	Late	Difficulty with veins
C	9	2	48	0	0	4	Late	Subject arrived late
C	9	2	72	0	0	7	Late	Subject arrived late

A = Geneva 2 x 20 mg fluoxetine HCl capsules (fasted)
B = Geneva 2 x 20 mg fluoxetine HCl capsules (fed)
C = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules (fed)

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Food - Study

TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Regimen	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Mi	Late/ Early	Reason/Comment
C	9	2	120	0	0	19	Late	Subject arrived late
C	9	2	336	0	0	5	Late	Subject arrived late
C	9	2	504					Sample time not recorded
C	11	2	48	0	1	25	Late	Subject arrived late
C	11	2	504					Did not show for blood draw
C	11	2	672					Did not show for blood draw
C	12	3	4	0	0	3	Late	Difficulty with veins
C	12	3	96	0	0	10	Late	Subject arrived late
C	12	3	672	0	0	15	Late	Subject arrived late
C	16	2	48	0	0	13	Late	Difficulty with veins
C	18	3	48					Did not show for blood draw
C	22	3	72	0	0	32	Early	Due to previous commitment
C	22	3	96	0	0	58	Early	Due to previous commitment
C	22	3	120	0	0	57	Early	Due to previous commitment
C	22	3	144	0	0	39	Early	Due to previous commitment
C	23	2	672					Sample time not recorded

A = Geneva 2 x 20 mg fluoxetine HCl capsules (fasted)
B = Geneva 2 x 20 mg fluoxetine HCl capsules (fed)
C = Dista (Prozac) 2 x 20 mg fluoxetine HCl Pulvules (fed)

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