CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75161

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-161 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Ticlopidine HCl Tablets, 250 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 23 Apparatus 2 (paddle) 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 45 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

Ticlopidine Hydrochloride
Tablets, 250 mg
ANDA: #75-161
Reviewer: F. Nouravarsani

Genpharm Inc.
Ontario, Canada
Submission Date:
March 02, 1998

Review of Amendments for Two Single-Dose Bioequivalence Studies, Dissolution Testing, and Recommendation for Approval

INTRODUCTION:

Genpharm had previously submitted two single-dose bioequivalence studies conducted under fasting and non-fasting conditions, and dissolution testing for its test product, Ticlopidine HCl Tablets, 250 mg, and the listed reference product, Ticlid Tablets, 250 mg (N19979-002, Oct. 31, 1991) manufactured by Syntex Inc. for Roche Laboratories.

Ticlopidine hydrochloride is a platelet aggregation inhibitor agent. It is freely soluble in water. Ticlopidine hydrochloride is rapidly absorbed following administration of a 250 mg single dose. An absorption of greater than 80% and peak plasma levels at about 2 hours has been reported (PDR, 1998).

Ticlopidine hydrochloride reversibly binds 98% to plasma proteins, primarily to serum albumin and lipoproteins. Ticlopidine hydrochloride is considerably metabolized by the liver, therefore only trace amounts of unchanged drug are found in the urine (PDR, 1998).

Ticlid is recommended to be taken with food to maximize its gastrointestinal tolerance. There is 20% increase in oral bioavailability of ticlopidine when taken after a meal (PDR, 1998).

DEFICIENCIES, RESPONSES, AND COMMENTS:

A. FASTING STUDY

1. Plasma concentrations at 16 - 120 hours were not submitted for subjects 1-24, reference product (Page 149 is duplicate copy of

page 148).

Response: The firm has submitted the missing page.

Comment: The response is acceptable.

2. AUC(0-Inf), Kel, and T1/2 were not calculated for subject #19, reference product.

Plasma concentration, ng/mL, at 48 hour for subject #19, reference product (reported in page 0182) was considered to be an anomaly. The firm was requested to clarify the reason that this sample was not reassayed.

Furthermore, the firm was requested to estimate the Kel with and without including the concentration at 48 hour, and then include the reference product's AUC(0-Inf) for this subject in the statistical data analysis and calculation of the 90% confidence intervals. The calculation of 90% confidence interval for lnAUC(0-T) was also requested after deleting the concentration at 48 hour.

Response:

The firm has responded that the plasma concentration at 48 hour for subject #19, reference product, was not considered an anomalous value by This concentration did not meet the criteria in SOP AL-1520-07, since it "was not two times higher nor % lower than the highest concentration on either of the two adjacent time points". There was not also any analytical reason to repeat this sample.

The Kel was estimated with and without including the plasma value at 48 hour. The calculated 90% CIs for ln-transformed AUC(0-Inf) and AUC(0-T) are as follows.

Parameters	90% CI (ln-transformed)
AUC(0-Inf), excluding subject #19 for the Reference product	102.2% - 119.8%
AUC(0-Inf) including subject #19 for the Reference product with the value at 48 hour	101.9% - 119.0%
AUC(0-Inf) including subject #19 for the Reference product without the value at 48 hour	102.2% - 119.3%
AUC(0-T) including subject #19 for the Reference product with the value at 48 hour	100.7% - 119.3%
AUC(0-T) including subject #19 for the Reference product without the value at 48 hour	100.9% - 119.5%

Comment:

The firm had apparently dropped subject #19's AUC(0-inf), Kel, and T1/2 for the reference product from the statistical data analyses because of the sample value at 48 hour. The reviewer believes that, this sample should have been reassayed for confirmation instead of excluding the subject from the data analysis.

However, the calculated 90% CIs for the AUC(0-Inf) and AUC(0-T) after including subject #19 with or without the value at 48 hour fall in the range of %.

The response is acceptable.

3. Statistical data analysis was requested to be submitted for each plasma sampling time using SAS - GLM procedure comparing the test and reference products under fasting conditions.

Response:

The firm has submitted results of the statistical data analysis

for each plasma sampling time. The data analyses for the 48 hour samples were performed with and without subject #19, reference product.

There is not a significant difference between the test and reference products at each sampling time, except for samples at 0.5, 1.0, 1.33, or 24 hours (p=0.05). This set of data included the sample value at 48 hour for subject #19, reference product. There is also a significant difference between the test and reference products at 48 hour (p=0.05), after excluding the sample value at 48 hour for subject #19, reference product.

Comment:

The response is acceptable.

B. NON-FASTING STUDY

1. Statistical data analysis was requested to be submitted for each plasma sampling time using SAS - GLM procedure comparing the test and reference products under non-fasting conditions, and the test product under fasting and non-fasting conditions.

Response:

The firm has submitted results of the statistical data analysis for each plasma sampling time.

Comment:

There is not a significant difference (p=0.05) between the test and reference products at each sampling time under the fed conditions.

There are significant differences (p=0.05) between the test product under fasting (Treatment A) and non-fasting (Treatment B) conditions at 1.67 and 2.0 hours (B<A), and at 3.0, 3.5, 4.0, 8.0, 24.0, and 96.0 hours (B>A).

The response is acceptable.

2. The statistical data analysis of ANOVA did not include sequence and subjects nested within sequence in the model. The

firm was requested to submit the results of ANOVA by including these factors.

Response:

The firm has performed statistical data analysis after including sequence and subjects nested within sequence in the model.

Comment:

Percentage ratios of the least-squares geometric means of the test and reference products under non-fasting conditions for AUC(0-T), AUC(0-Inf), and C(Max) were 112.0%, 112.6%, and 118.0%, respectively (Table 1).

Percentage ratios of the least-squares geometric means of the test product under non-fasting and fasting conditions for AUC(0-T), AUC(0-Inf), and C(Max) were 112.8%, 112.5%, and 97.8%, respectively (Table 1). Percentage ratios of the least-squares means are also shown in Table 1.

The response is acceptable.

C. DISSOLUTION TESTING

The Division of Bioequivalence recommended dissolution testing to be conducted on 12 units for each of the test and reference products using the following method and specifications:

Apparatus: USP paddle, 50 RPM
Medium: Water
Volume: 900 mL
Tolerance: NLT % (Q) in 45 minutes

Response:

Dissolution testing was conducted on 12 units of each the test and reference products in 900 mL water at 37° C using apparatus 2 at 50 rpm. Not less than % (Q) of the labeled amount of Ticlopidine was dissolved in 45 minutes for each, the test or reference product. No unit was less than Q % (Table 2).

Comment:

The response is acceptable.

COMMENTS:

A. FASTING STUDY

1. The 90% confidence intervals (CIs) for the least-squares means, ln-transformed parameters of AUC(0-T), AUC(0-Inf), and C(Max) fall within the range % required by the Division of Bioequivalence. The AUC(0-Inf) was not included for subject #19, reference product.

The calculated 90% CIs for the AUC(0-Inf) and AUC(0-T) after including subject #19 for the reference product with or without the value at 48 hours fall also in the range of %.

2. There was a statistically significant sequence effect ($p<0.1$) for the ln-transformed AUC(0-Inf) [the plasma level at 48 hours for subject #19, reference product was excluded], AUC(0-T), and C(Max).

However, according to the Division of Bioequivalence Guidance titled: "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design" (July 01, 1992) the sequence effect may be acceptable since the following were met:

a) The study was a single dose study;
b) Only healthy, normal subjects completed the study;
c) The drug was not an endogenous entity;
d) Washout period of two weeks was long enough between the two phases, and there was no detectable Ticlopidine level in predose samples of any of the subjects;
e) All scientific and statistical criteria were met;
f) The assay methodology was valid and acceptable;
g) The data were acceptable; and
h) Statistical data analyses were appropriate and the parameters met the confidence intervals criteria.

B. NON-FASTING STUDY:

1. The percentage ratios of the least-squares geometric means of

the test and reference products under non-fasting conditions for AUC(0-T), AUC(0-Inf), and C(Max) fall in the acceptable range.

2. The percentage ratios of the least-squares geometric means of the test product under non-fasting and fasting conditions for AUC(0-T), AUC(0-Inf), and C(Max) were 112.8%, 112.5%, and 97.8%, respectively.

C. DISSOLUTION TESTING

The firm conducted dissolution testing using the method recommended by the Division of Bioequivalence.

DEFICIENCY (CURRENT SUBMISSION): None.

RECOMMENDATIONS:

A. FASTING STUDY

The fasting bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its Ticlopidine HCl, 250 mg, Tablets, Bulk #103576 (Lot #103743) comparing it to Roche Laboratories (Syntex), Ticlid, 250 mg, Tablets, Lot #07525A has been found acceptable by the Division of Bioequivalence.

B. NON-FASTING STUDY

The non-fasting bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its Ticlopidine HCl, 250 mg, Tablets, Bulk #103576 (Lot #103743) comparing it to Roche Laboratories (Syntex), Ticlid, 250 mg, Tablets, Lot #07525A has been found acceptable by the Division of Bioequivalence.

C. DISSOLUTION TESTING

The dissolution testing conducted by the Genpharm Inc. Pharmaceuticals on its Ticlopidine HCl, 250 mg, Tablets, Bulk #103576 (Lot #103740), and Ticlid, 250 mg, Tablets, Lot #07525A has been found acceptable.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP

23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than ⅛ (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

D. RECOMMENDATION FOR APPROVAL:

From the bioequivalence point of view the firm has met the requirements of in vivo bioequivalency and in vitro dissolution testing.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED BDAVIT 8/5/98
FT INITIALED BDAVIT /S/ 8/6/98

Concur: /S/ Date: 8/7/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table 1: **Non-Fasting Study**

Ratio of Least-Squares Means (Geometric):

	Test(Fed)/Ref.(Fed)	Test(Fed)/Test(Fast)
AUC(0-T)	112.03%	112.84%
AUC(0-Inf)	112.63%	112.50%
C(Max)	118.02%	97.77%

Ratio of Least-Squares Means:

	Test(Fed)/Ref.(Fed)	Test(Fed)/Test(Fast)
AUC(0-T)	%110.68	%112.56
AUC(0-Inf)	%112.93	%112.83
C(Max)	%111.40	%98.67

APPEARS THIS WAY
ON ORIGINAL

Table 2: In Vitro Dissolution Testing

Drugs (Generic Name): Ticlopidine HCL Tablets
Dose Strength: 250 mg
ANDA: #75-161
Firm: Genpharm
Submission Date: March 02, 1998

I. Conditions for Dissolution Testing:

USP XXIII Basket____ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

Reference Drug: Ticlid Tablets, 250 mg

Assay Methodology: _____

Tolerances: NLT % dissolved at 45 minutes

Method: FDA

II. Results of In Vitro Dissolution Testing:

Sampling Times minutes	Test Product: Bulk Lot# 103576 (lot#103740) Strength (mg) 250			Reference Product: Lot #07525A Strength (mg) 250		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
05	95.4	_	(2.1)	29.1	_	(29.1)
10	99.2	_	(1.6)	78.1	_	(16.8)
15	100.1	_	(1.5)	96.4	_	(5.4)
20	100.5	_	(1.5)	101.4	_	(4.1)
30	100.8	_	(1.4)	103.6	_	(3.1)
45	100.1	_	(1.7)	102.6	_	(2.5)

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-161 APPLICANT: Genpharm, Inc. JAN 8 1998

DRUG PRODUCT: Ticlopidine Hydrochloride Tablets, 250 mg

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

A. FASTING STUDY

1. Plasma concentrations at 16 - 120 hours were not submitted for subjects 1-24, reference product (Page 149 is duplicate copy of page 148).

2. AUC(0-Inf), Kel, and T1/2 were not calculated for subject #19, reference product, period 1.

   Plasma concentration, ng/mL, at 48 hours for subject #19, reference product (reported in page 0182) is considered to be an anomaly. Please clarify the reason why this sample was not reassayed.

   Furthermore, please estimate the Kel by including and excluding the concentration at 48 hours, and then include the reference product's AUC(0-Inf) for this subject in the statistical data analysis and calculation of the 90% confidence interval. The 90% confidence interval should also be re-calculated for AUC(0-T), when the concentration at 48 hours is omitted.

3. Please submit statistical data analysis for each plasma sampling time using SAS - GLM procedure comparing the test and reference products under fasting conditions.

B. NON-FASTING STUDY

1. Please submit statistical data analysis for each plasma sampling time using SAS - GLM procedure comparing the test and reference products under non-fasting conditions, and the test product under fasting and non-fasting conditions.

2. The statistical data analysis of ANOVA did not include sequence and subjects nested within sequence in the model. Please submit the results of ANOVA by including these factors.

C. DISSOLUTION TESTING

The Division of Bioequivalence recommends dissolution testing to be conducted on 12 units for each of the test and reference products using the following method and specifications:

Apparatus: USP paddle, 50 RPM
Medium: Water
Volume: 900 mL
Tolerance: NLT % (Q) in 45 minutes

Sincerely yours,

/S/

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

Ticlopidine Hydrochloride
Tablets, 250 mg
ANDA: #75-161
Reviewer: F. Nouravarsani

Genpharm Inc.
Ontario, Canada
Submission Date:
July 08, 1997

Review of Two Single-Dose Bioequivalence Studies Under Fasting and Non-Fasting Conditions, and Dissolution Testing

INTRODUCTION:

Genpharm has submitted two single-dose bioequivalence studies conducted under fasting and non-fasting conditions, and dissolution testing for its test product, Ticlopidine HCl Tablets, 250 mg, and the listed reference product, Ticlid Tablets, 250 mg (N19979-002, Oct. 31, 1991) manufactured by Syntex Laboratories, Inc., which has been purchased by Hoffman-LaRoche.

Ticlopidine hydrochloride is a platelet aggregation inhibitor agent. It is freely soluble in water. Ticlopidine hydrochloride is rapidly absorbed following administration of a 250 mg single dose. An absorption of greater than 80% and peak plasma levels at about 2 hours has been reported (PDR, 1997).

Ticlopidine hydrochloride reversibly binds 98% to plasma proteins, primarily to serum albumin and lipoproteins. Ticlopidine hydrochloride is considerably metabolized by the liver, therefore only trace amounts of unchanged drug are found in the urine (PDR, 1997).

Ticlid is recommended to be taken with food to maximize its gastrointestinal tolerance. There is 20% increase in oral bioavailability of ticlopidine when taken after a meal (PDR, 1997).

I. SINGLE-DOSE STUDY UNDER FASTING CONDITIONS:

Objective:

Comparison of the test and reference products under fasting conditions.

Sponsor: Genpharm Inc., Etobicoke, Ontario
Study Site:

Study Design:

A single-dose of the test and reference products, each was administered randomly to healthy adult male volunteers in a two - way crossover study design under fasting conditions (study report #960140).

Treatments:

Treatment A: Ticlopidine HCl, 1X250 mg Tablet, bulk #103576, lot #103743, batch size tablets (yield batch size of tablets).

Treatment B: Ticlid, 1X250 mg Tablet, lot #07525A, expiration date: June 1998.

Clinical Study Dates:

Phase I: November 27, 1996
Phase II: December 11, 1996
Washout period: Fourteen (14) days.

Subjects:

Forty-three (43) healthy adult male volunteers were enrolled in the study. Two subjects did not complete the study (subject #25 was dropped by the Medical Director after period 1 due to positive urine drug screen for cannabinoids, and subject #36 dropped for personal reasons after period 1). Therefore, forty-one (41) subjects completed the study. However, the samples from 40 subjects were assayed as per protocol (4 subjects were alternates). The range of subjects age, weight, and height are summarized as follows:

Age: 18-44 years
Weight: 61.0-85.8 kg
Height: 163-186 cm

Housing, Fasting/Meals:

The subjects were housed from 12 hours before, and until 36 hours after the dose. The subjects fasted overnight prior to the dosing and 4.0 hours after the dose. Standard meals were served for both periods. The subjects were allowed to drink water ad lib, except within one hour of the dose administration. However, the dose was taken with 240 mL water.

Blood Samples:

Blood samples were collected at pre-dose and at 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 120 hours post-dose.

Analytical Procedures:

Limit of Quantitation:

The limit of quantitation was determined to be ng/mL.

Linearity: ng/mL, weighting factor = 1/conc.

Specificity: specific

Internal Standard: Imipramine

Accuracy (During Study):

Interday from Standard Samples:
range of ng/mL: %

Interday from QC samples: ng/mL
ng/mL
ng/mL

Precision (During Study):

Interday CV% from Standard Samples:
range of ng/mL:

Interday CV% from QC samples: ng/mL
ng/mL
ng/mL

Recovery:

Ticlopidine: ng/mL (CV%=6, N=6)
ng/mL (CV%=5.1, N=6)
ng/mL (CV%=9.1, N=6)
Internal Standard: ug/mL (CV%=11, N=6)

Stability Studies:

Long-Term: The frozen plasma stability study period, 152 days, at -22° C for the analytes covered the length of clinical and analytical study. The study samples were stored at -22° C for a duration of not exceeding 62 days.

Short-Term (benchtop): samples kept at 22° C for 6.5 hours were found stable.

Freeze-Thaw: samples were found stable after four freeze-thaw cycles.

Autosampler: stable for 17.3 hours kept at 4° C. The samples were also found stable in a extended autosampler stability study conducted at 4° C for 62.2 hours.

Statistical Analysis:

The data from Ticlopidine were analyzed using SAS-GLM procedure. The two one sided t-test procedure (90% confidence intervals) was used to compare the ln-transformed (least-squares means) pharmacokinetic parameters of AUC(0-T), AUC(0-Inf), and C(Max) obtained from the test and reference products. The ratios of the geometric least-squares means were also calculated for the parameters.

Results:

The mean plasma concentrations of Ticlopidine obtained for the test and reference products are summarized in Table 1. Plots of the un-transformed and ln-transformed mean plasma concentrations of Ticlopidine versus time for both, test and reference products are shown in Figures 1 and 2. The mean of the pharmacokinetic parameters obtained for both, test and reference products are compared in Table 2.

The test product AUC(0-T) and AUC(0-Inf), 1508.2 hr*ng/mL and 1593.9 hr*ng/mL, respectively, are comparable with those obtained for the reference product, 1384.8 hr*ng/mL and 1471.0 hr*ng/mL, respectively. Range of percentage ratio of AUC(0-T)/AUC(0-Inf) is 74.1-97.4 for the test product, and 86.3-98.1 for the reference product (Table 3).

The mean C(Max) value of 496.15 ng/mL obtained for the test product is also comparable with the mean C(Max) value of 449.35 ng/mL obtained for the reference product.

The mean percentage of test/reference for the parameters of AUC(0-T), AUC(0-Inf), and C(Max) is 114.6, 114.8, and 119.3, respectively (Table 4).

The 90% confidence intervals (CI) for the least-squares means, (ln-transformed) parameters of AUC(0-T), AUC(0-Inf), and C(Max) fall within the range (80% - 125%) required by the Division of Bioequivalence (Table 2).

There was a statistically significant formulation effect ($p<0.05$) for the ln-transformed AUC(0-Inf).

There was a statistically significant sequence effect ($p<0.1$) for the ln-transformed AUC(0-T) and C(Max).

Medical Events:

Medical events, which were possibly drug related are as follows:

Subject	Medical Event	Product
10	nausea	test
22	nausea	test
30	nausea	test
33	nausea	test
14	dizziness	test
22	dizziness	test
30	dizziness	test
33	dizziness	test
28	gas in stomach	test
33	vomiting intermittent (1.6 days after dosing)	test
10	intermittent flatulence	reference

II. SINGLE-DOSE STUDY UNDER NON-FASTING CONDITIONS:

Objectives:

1. Comparison of the test and reference products under non-fasting conditions.

2. Comparison of the test product under non-fasting and fasting conditions.

Sponsor: Genpharm Inc., Etobicoke, Ontario
Study Site:

Study Design:

A single-dose of the test and reference products under non-fasting, and the test product under fasting conditions, each was administered randomly to healthy adult male volunteers in a three - way crossover study design (study report #960139).

Treatments:

Treatment A: Ticlopidine HCl, 1X250 mg Tablet, bulk No. 103576, lot #103743 was administered under fasting conditions.

Treatment B: Ticlopidine HCl, 1X250 mg Tablet, bulk No. 103576, lot #103743 was administered under non-fasting conditions.

Treatment C: Ticlid, 1X250 mg Tablet, lot #07525A (expiration date: June 1998) was administered under non-fasting conditions.

Clinical Study Dates:

Phase I: February 11, 1997
Phase II: February 25, 1997
Phase III: March 11, 1997
Washout period: Fourteen (14) days.

Subjects:

Eighteen (18) healthy adult male volunteers were enrolled in the study. Two subjects did not complete the study (subject #2 and

#3 dropped before the period 2 for personal reasons). The range of subjects age, weight, and height are:

Age: 20-42 years; Weight: 62.3-86.9 kg; Height: 166-189 cm

Housing, Fasting/Meals:

The subjects were housed from evening before, and until 36 hours after the dose. The subjects fasted overnight until 30 minutes before the dose for the non-fasting study, when a standard breakfast was served. The subjects fasted overnight prior to the dosing and 4.0 hours after the dose for the fasting study. Standard meals were served for both periods during the housing. The subjects were allowed to drink water ad lib, except within one hour of the dose administration. However, the dose was taken with 240 mL water.

Blood Samples:

Blood samples were collected at pre-dose and at 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 120 hours post-dose.

Analytical Procedures:

Limit of Quantitation:

The limit of quantitation was determined to be ng/mL.

Linearity: ng/mL, weighting factor = 1/conc.

Specificity: specific

Internal Standard: Imipramine

Accuracy (During Study):

Interday from Standard Samples:
range of ng/mL: %

Interday from QC samples: ng/mL
ng/mL
ng/mL

Precision (During Study):

Interday CV% from Standard Samples:
range of ng/mL: %

Interday CV% from QC samples: ng/mL
ng/mL
ng/mL

Recovery:

Ticlopidine: ng/mL (CV%=6, N=6)
ng/mL (CV%=5.1, N=6)
ng/mL (CV%=9.1, N=6)

Internal Standard: % for ug/mL (CV%=11, N=6)

Stability Studies:

Long-Term: The frozen plasma stability study period, 152 days, at -22° C for the analytes covered the length of clinical and analytical study. The study samples were stored at -22° C for a duration of not exceeding 79 days.

Short-Term (benchtop): samples kept at 22° C for 6.5 hours were found stable.

Freeze-Thaw: samples were found stable after four freeze-thaw cycles.

Autosampler: stable for 17.3 hours kept at 4° C. The samples were also found stable in an extended autosampler stability study conducted at 4° C for 62.2 hours.

Statistical Analysis:

The data from Ticlopidine were analyzed using SAS-GLM procedure for un-transformed and ln-transformed pharmacokinetic parameters of AUC(0-T), AUC(0-Inf), and C(Max) obtained from the test and reference products. The ANOVA model included subjects, period, drug formulation, and first-order carryover. A 5% level of significant was used. The ratios of least-squares means were calculated using un-transformed and ln-transformed values of the parameters comparing treatment B versus treatment A, and treatment B versus treatment C.

Results:

The mean plasma Ticlopidine concentrations are summarized in Table 5. Linear and ln-transformed Plots of the mean plasma concentrations of Ticlopidine versus time for the test-fed, reference-fed, and test-fasted are shown in Figures 3 and 4. The pharmacokinetic parameters are compared in Table 6.

The AUC(0-T) for the test (fed) product, 1920.5 hr*ng/mL, is comparable with the AUC(0-T) of 1741.6 hr*ng/mL for the reference (fed) product.

The AUC(0-Inf) for the test (fed) product, 2002.3 hr*ng/mL, is comparable with the one obtained for the reference (fed) product, 1746.2 hr*ng/mL.

Range of percentage ratio of AUC(0-T)/AUC(0-Inf) is 82.1-97.7 for the test product under fasting conditions, 92.0-97.7 for the test product under non-fasting conditions, and 80.5-97.1 for the reference product under non-fasting conditions (Table 7).

The C(Max) for the test (fed) product, 540.5 ng/mL, is comparable with the C(Max) of 487.3 ng/mL for the reference (fed) product.

Percentage ratios of the least-squares geometric means of the test and reference products under non-fasting conditions for AUC(0-T), AUC(0-Inf), and C(Max) were 111.5%, 112.5%, and 116.2%, respectively (Table 8).

Percentage ratios of the least-squares geometric means of the test product under non-fasting and fasting conditions for

AUC(0-T), AUC(0-Inf), and C(Max) were 113.6%, 114.6%, and 100.4%, respectively (Table 8).

Medical Events:

Medical events were reported as follows:

Subject	Medical Event	Product	Drug Related
01	headache	test (fasting)	possible
01		test (fed)	possible
13		test (fed)	possible
04		ref. (fed)	possible
04	dizziness	test (fasting)	possible
04		test (fed)	possible
04		ref. (fed)	possible
12		ref. (fed)	possible
14		ref. (fed)	possible
01	abdominal pain	test (fed)	possible
09	stomach pains	test (fed)	Possible
14	belly hurts	ref. (fed)	possible
04	heartburn	ref. (fed)	possible
12	stomach cramps	ref. (fed)	probable
01	loose stools	test (fed)	possible
09		test (fed)	possible
14	intermittent loose stools	ref. (fed)	possible
04	feels tired	test (fed)	possible
14	nausea	ref. (fed)	possible

III. DISSOLUTION TESTING:

The firm submitted dissolution testing conducted on 12 units for each of the test and reference products in 500 mL of aqueous solution of HCl and NaCl. The apparatus was paddle at 75 RPM. The results are summarized in Table 9.

The Division of Bioequivalence recommends the following dissolution testing method and specifications (E-Mail from Larry Ouderkirk, 12/07/1995):

Apparatus: USP paddle, 50 RPM
Medium: Water
Volume: 900 mL
Tolerance: NLT % (Q) in 45 minutes

Assay Potency:

The potencies were 98.6% and 97.6% for the test and reference products, respectively. Formulations of the test and reference products are compared in Table 10.

Content Uniformity:

The mean content uniformity was 99.7% (CV%=0.51) for the test product.

COMMENTS:

A. FASTING STUDY

1. Forty-three (43) healthy adult male volunteers including four (4) alternates were enrolled in the study. However, the samples from 40 subjects (subjects #1-24, 26-35, 37-39, 41-42 and 44) were assayed as per protocol.

2. Six (6) Plasma samples were not obtained during period 2 for the test product: subject #11 (48 hr); subject #15 (96 hr, 120 hr); subject #19 (96 hr); subject #33 (72 hr, 96 hr).

B. NON-FASTING STUDY

1. Kel, AUC(0-Inf), and T1/2 could not be estimated for subject #13, period 2, treatment C.

2. The standard breakfast used in the food-effect study was the same as the breakfast recommended by the Division of Bioequivalence (memo dated May 24, 1991).

C. DISSOLUTION TESTING

There is no dissolution testing method listed for Ticlopidine HCl Tablets in the USP 23/NF 18 (1995 and supplements).

DEFICIENCIES:

A. FASTING STUDY

1. Plasma concentrations at 16 - 120 hours were not submitted for subjects 1-24, reference product (Page 149 is duplicate copy of page 148).

2. AUC(0-Inf), Kel, and T1/2 were not calculated for subject #19, reference product, period 1.

Plasma concentration, ng/mL, at 48 hours for subject #19, reference product (reported in page 0182) is considered to be an anomaly. The firm should clarify the reason that, this sample was not reassayed.

Furthermore, the firm should estimate the Kel by including and excluding the concentration at 48 hours, and then include the reference product's AUC(0-Inf) for this subject in the statistical data analysis and calculation of the 90% confidence interval. The 90% confidence interval should also be re-calculated for AUC(0-T), when the concentration at 48 hours is omitted.

3. Statistical data analysis should be submitted for each plasma sampling time using SAS - GLM procedure comparing the test and reference products under fasting conditions.

B. NON-FASTING STUDY

1. Statistical data analysis should be submitted for each plasma sampling time using SAS - GLM procedure comparing the test and reference products under non-fasting conditions, and the test

product under fasting and non-fasting conditions.

2. The statistical data analysis of ANOVA did not include sequence and subjects nested within sequence in the model. The firm should submit the results of ANOVA by including these factors.

C. DISSOLUTION TESTING

The Division of Bioequivalence recommends dissolution testing to be conducted on 12 units for each of the test and reference products using the following method and specifications:

Apparatus: USP paddle, 50 RPM
Medium: Water
Volume: 900 mL
Tolerance: NLT % (Q) in 45 minutes

RECOMMENDATIONS:

A. FASTING STUDY

The fasting bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its Ticlopidine HCl, 250 mg, Tablets, Bulk #103576 (Lot #103743) comparing it to Roche Laboratories (Syntex), Ticlid, 250 mg, Tablets, Lot #07525A has been found incomplete by the Division of Bioequivalence.

B. NON-FASTING STUDY

The non-fasting bioequivalence study submitted by Genpharm Inc. Pharmaceuticals on its Ticlopidine HCl, 250 mg, Tablets, Bulk #103576 (Lot #103743) comparing it to Roche Laboratories (Syntex), Ticlid, 250 mg, Tablets, Lot #07525A has been found incomplete by the Division of Bioequivalence.

C. DISSOLUTION TESTING

The dissolution testing conducted by the Genpharm Inc. Pharmaceuticals on its Ticlopidine HCl, 250 mg, Tablets, Lot #103576, and Ticlid, 250 mg, Tablets, Lot #07525A has been found incomplete.

The firm should be informed of the **DEFICIENCIES under A, B, and C**, and the **RECOMMENDATIONS under A, B, and C**.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 12/16/97

Concur: /S/ Date: 12/31/97
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA #75-161 (original, duplicate), Nouravarsani, HFD-658, Drug File, Division File

Table 1: **FASTING STUDY**

Arithmetic Mean Plasma Concentrations (ng/mL) of Ticlopidine, N=40

Time, hr	Test Product	Reference Product
0.00	0.00 (--)	0.00 (--)
0.50	26.282(168)	10.671(200)
1.00	207.183(83)	142.874(103)
1.33	340.894(66)	263.392(76)
1.67	422.404(54)	360.459(66)
2.00	424.662(58)	379.796(58)
2.33	345.053(75)	321.684(58)
2.67	276.231(89)	270.703(67)
3.00	199.199(84)	211.947(75)
3.50	143.387(92)	149.709(102)
4.00	100.165(80)	110.073(95)
6.00	40.588(78)	39.102(85)
8.00	28.179(75)	26.139(70)
12.00	16.544(69)	15.874(67)a
16.00	12.031(61)a	11.100(63)
24.00	7.909(60)	7.317(66)
36.00	4.861(66)	4.643(82)
48.00	3.082(90)a	2.665(101)a
72.00	1.183(154)a	1.139(166)
96.00	0.718(197)b	0.542(252)
120.00	0.516(223)a	0.357(273)

a: N = 39
b: N = 36

Table 2: **FASTING STUDY**

Comparison of Arithmetic Mean (CV%) Ticlopidine Pharmacokinetic Parameters, and 90% CI Obtained for 250 mg Tablets of the Test and Reference Products, N=40:

Parameters	Test	Reference	90% CI(ln-trans.)
AUC(0-T) hr*ng/mL	1508.2(68.9)	1384.8(69.6)	100.7% - 119.3%
AUC(0-Inf) hr*ng/mL	1593.9(67.6)	1471.0(68.4)a	102.2% - 119.8%
C(Max) ng/mL	496.15(55.6)	449.35(54.1)	99.4% - 123.2%
T(Max) hr	1.801 (17.2)	1.988 (23.4)	
K(Elm) 1/hr	0.0378(41.3)	0.0449(45.1)a	
T(1/2) hr	22.06 (47.5)	18.81 (47.6)a	

a: N=39

Table 3: **FASTING STUDY**, AUC(0-T)/AUC(0-Inf) Percentage:

Subject	Test	Reference
01		
02		
03		
04		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
26		
27		
28		
29		
30		
31		
32		
33		
34		
35		
37		
38		
39		
41		
42		
44		
Mean%	93.54	94.02
CV%	4.2	2.9
Range%		
N	40	39

Table 4: **FASTING STUDY**, Ratio of the Test/Ref Percentage:

Subject	AUC(0-T)	AUC(0-Inf)	C(Max)
01			
02			
03			
04			
05			
06			
07			
08			
09			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
37			
38			
39			
41			
42			
44			
Mean%	114.6	114.83	119.3
CV%	30.9	29.7	41.0
Range%			
N	40	39	40

Table 5: **NON-FASTING STUDY**

Comparison of Arithmetic Mean (CV%) Ticlopidine Plasma Concentrations (ng/mL) of the Test and Reference Products, N = 16:

Time, hr	Test (Fast)	Test (Fed)	Ref. (Fed)
0.00	0.00 (---)	0.00 (---)	0.00 (---)
0.50	42.47 (142)	29.44 (234)	8.10 (128) a
1.00	220.83 (72)	168.32 (141)	129.84 (145)
1.33	377.53 (56)	228.10 (122)	233.62 (155)
1.67	483.75 (50)	258.14 (86)	275.63 (113)
2.00	467.80 (42)	325.14 (53)	297.00 (81)
2.33	371.37 (52)	357.61 (58)	310.01 (61)
2.67	298.49 (69)	374.33 (72)	314.83 (60)
3.00	222.91 (73)	364.56 (79)	275.95 (56)
3.50	151.10 (86)	281.50 (84)	231.57 (70)
4.00	111.57 (82)	205.55 (86)	186.84 (89)
6.00	48.04 (70)	75.10 (102)	73.86 (132)
8.00	31.99 (79)	38.14 (86)	35.30 (97)
12.00	20.58 (72)	21.87 (82)	20.52 (76)
16.00	15.30 (71)	16.38 (72)	15.06 (75)
24.00	9.62 (66)	11.12 (69)	10.08 (70)
36.00	6.05 (76)	6.87 (69)	6.90 (74)
48.00	3.86 (73) a	3.67 (83)	3.65 (76)
72.00	1.50 (147)	1.81 (107)	1.99 (116)
96.00	0.48 (300)	1.11 (138)	1.24 (157)
120.0	0.28 (400)	0.79 (156)	0.77 (186)

a: N=15

Table 6: **NON-FASTING STUDY**

Comparison of Arithmetic Mean (CV%) Ticlopidine Pharmacokinetic Parameters of the Test and Reference Products, N=16:

Parameters	Test(Fast)	Test(Fed)	Ref.(Fed)
AUC(0-T) hr*ng/mL	1712.3(61)	1920.5(65)	1741.6(66)
AUC(0-Inf) hr*ng/mL	1786.4(61)	2002.3(63)	1746.2(67)a
C(Max) ng/mL	552.03(46)	540.5 (53)	487.26(63)
T(Max) hr	1.856 (17)	2.167(34)	2.365(34)
K(Elm) 1/hr	0.0437(34)	0.0409(72)	0.0401(57)a
T(1/2) hr	17.76 (38)	22.15 (43)	21.17(42)a

a: N=15

Table 7: **NON-FASTING STUDY**, AUC(0-T)/AUC(0-Inf) Percentage, N=16

Subject	Test(Fast)	Test(Fed)	Ref.(Fed)
1			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
Mean%	94.7	95.2	93.9
CV%	4.0	1.8	4.3
Range%			
N	16	16	15

Table 8: **NON-FASTING STUDY**

Ratio of Least-Squares Means **(Geometric)**:

	Test(Fed)/Ref.(Fed)	Test(Fed)/Test(Fast)
AUC(0-T)	111.5%	113.6%
AUC(0-Inf)	112.5%	114.6%
C(Max)	116.2%	100.4%

Ratio of Least-Squares Means:

	Test(Fed)/Ref.(Fed)	Test(Fed)/Test(Fast)
AUC(0-T)	110.9%	113.6%
AUC(0-Inf)	113.3%	115.5%
C(Max)	108.9%	100.6%

Table 9: **In Vitro Dissolution Testing**

Drug (Generic Name): Ticlopidine HCl Tablets
Dose Strength: 250 mg
ANDA #75161
Firm: Genpharm Inc. Pharmaceuticals
Submission Date: July 08, 1997

I. Conditions for Dissolution Testing:

USP XXIII Basket ___ Paddle X RPM 75 No. Units Tested 12

Medium: HCl Acid/Na Cl at 37° C Volume: 500 mL

Reference Drugs: Ticlid, 250 Tablets, Roche

Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

Sampling Times minutes	Test Product: Lot #103576 Strength (mg) 250			Reference Product: Lot #07525A Strength (mg) 250		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
05	87.9	-	(08.5)	50.6	-	(30.8)
10	97.9	-	(02.7)	86.3	-	(04.5)
15	99.1	-	(02.3)	93.6	-	(03.0)
20	99.4	-	(02.4)	95.2	-	(03.5)
25	99.5	-	(02.4)	95.8	-	(03.6)
30	99.8	-	(02.4)	96.3	-	(03.5)

Table 10: Formulations Comparison of the Test and Reference products

Ingredients	Test, mg	Ref., mg (a)
Ticlopidine HCl	250.0	250.0
Microcrystalline Cellulose		
Povidone		
Starch		
Ammonium Chloride		
Stearic Acid		
Magnesium Stearate		
Tablet Weight		
Coating:		
Hydroxypropylmethyl Cellulose		
Titanium Dioxide		
Lactose Monohydrate		
Triacetin		
Ink Used by Innovator for Tablet Marking:		

---

a: From the PDR (1997)
X: Present in the product

Figure 1

Project No. 960140

Mean Plasma Ticlopidine Concentrations

(Linear Plot)

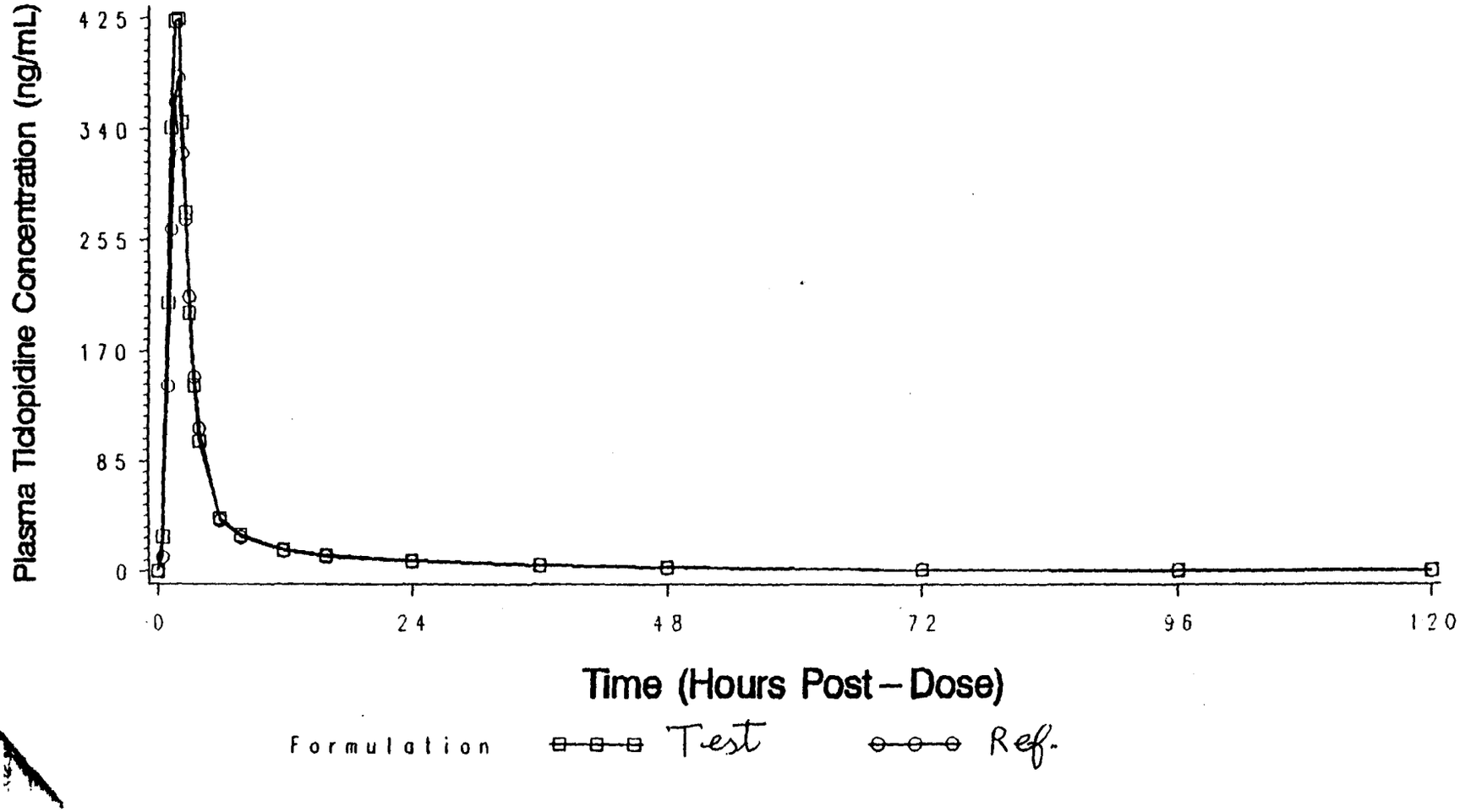

Figure 2

Project No. 960140

Mean Plasma Ticlopidine Concentrations

(Semi – Log Plot)

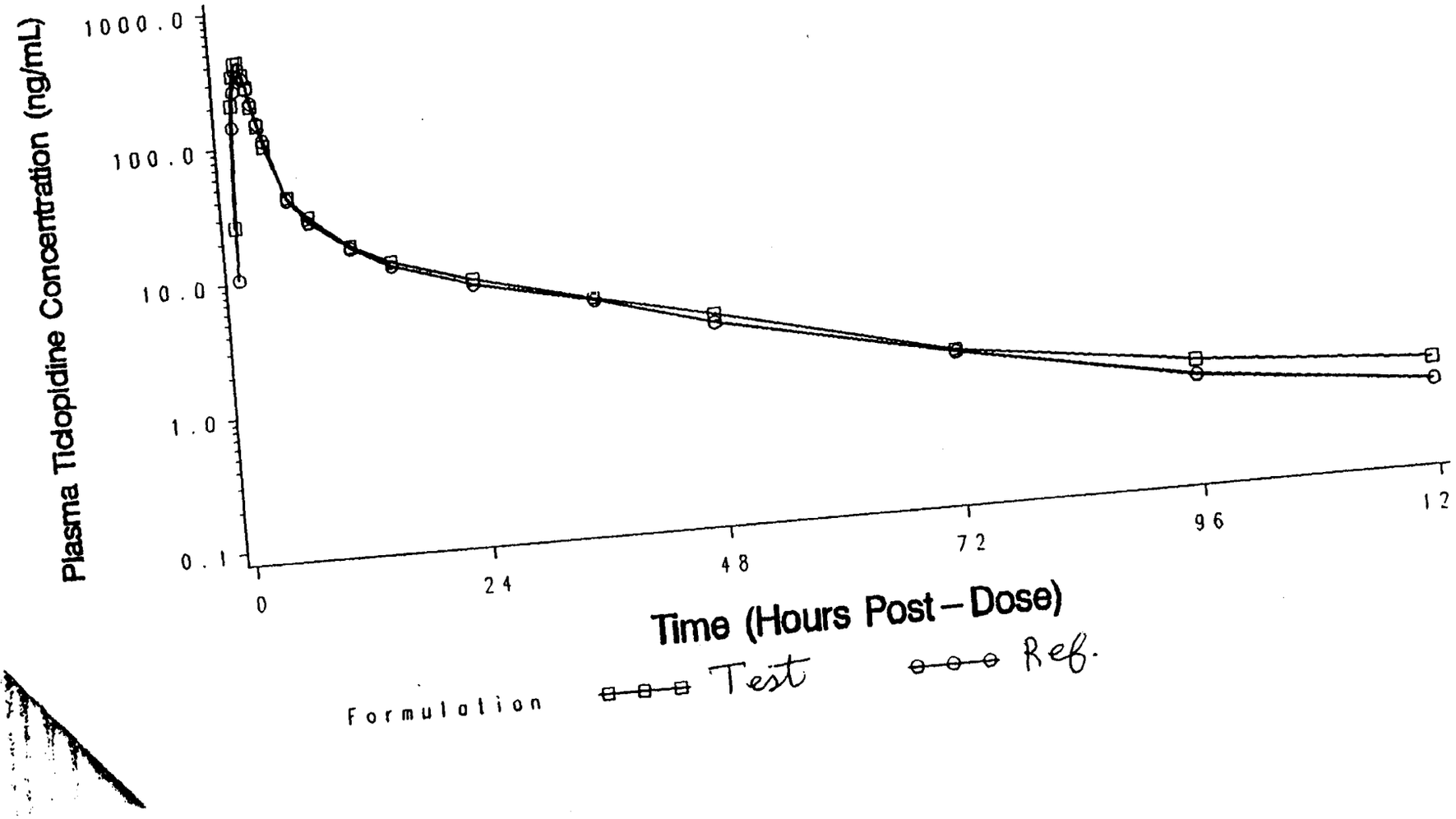

Figure 3

Project No. 960139

Mean Plasma Ticlopidine Concentrations

(Linear Plot)

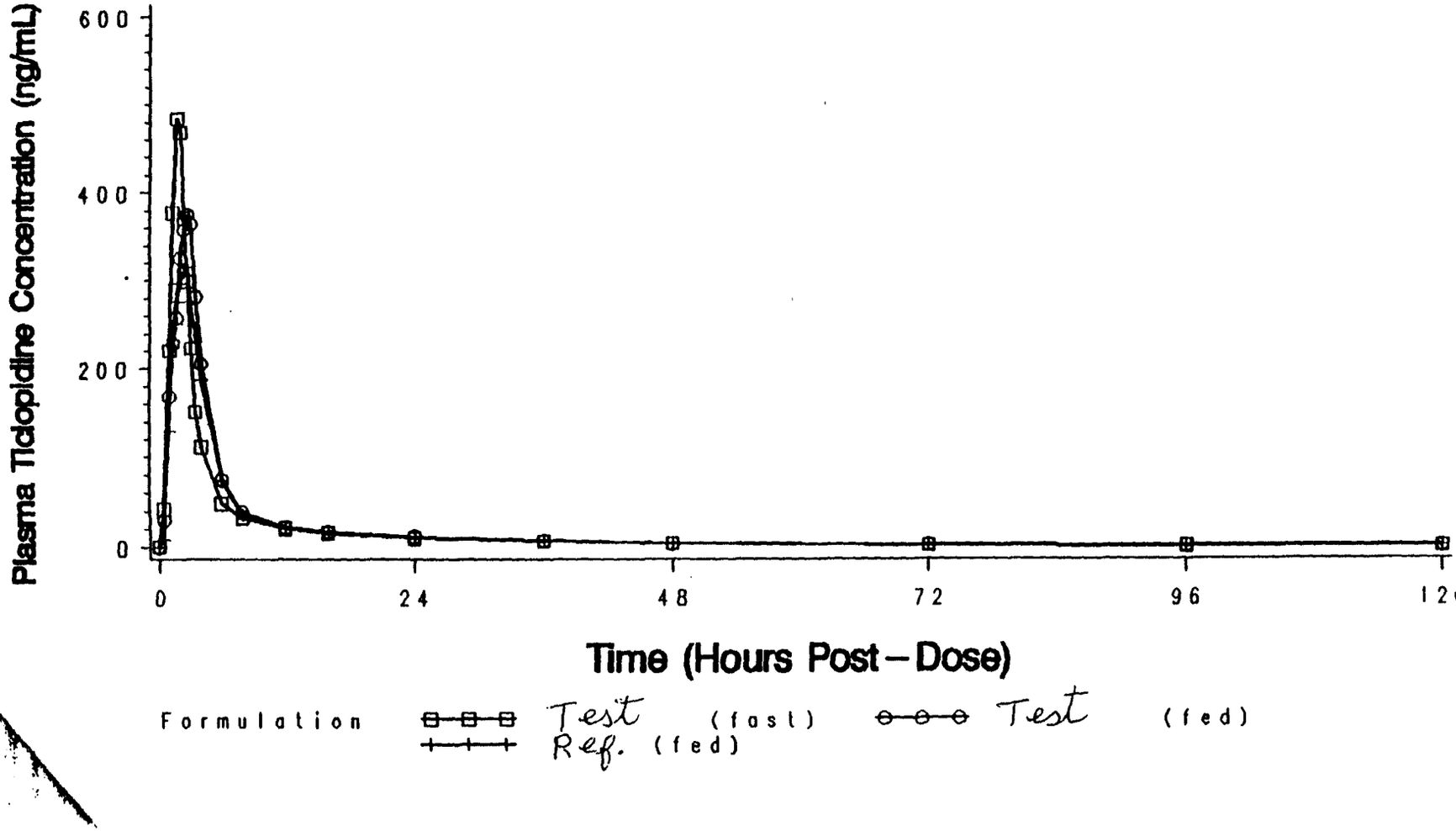

Figure 4

Project No. 960139

Mean Plasma Ticlopidine Concentrations

(Semi – Log Plot)