CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-188

BIOEQUIVALENCE

Amiodarone HCl
Tablets, 200 mg
ANDA #75-188
Reviewer: F. Nouravarsani
75188SDA.298

Alphapharm PTY. LTD.
Australia
Submission Dates:
February 12, 1998
July 30, 1998
August 19, 1998, and
August 27, 1998

REVIEW OF AMENDMENTS FOR SINGLE DOSE BIOEQUIVALENCE STUDY, DISSOLUTION TESTING, AND RECOMMENDATION FOR APPROVAL

Alphapharm had previously submitted a single dose bioequivalence study conducted under fasting conditions on its test product, Amiodarone HCl Tablets, 200 mg and the listed reference product, Wyeth-Ayerst's Cordarone Tablets, 200 mg (NDA #18972, December 24, 1985).

In the current submissions the firm has responded to the deficiencies as follows:

1. The firm had stated that "results from rejected batches, if any, are not included in the report".

The DBE requested that the rejected runs (if any) and the reason(s) for rejecting to be submitted.

Response: The firm submitted the rejected runs and the reasons for rejecting them as it follows:

Run GLN07 (subject #5): The run was rejected for the metabolite, Desethylamiodarone, because there were no peaks for standard samples B and C. The standard sample D was also rejected, since its deviation from the nominal concentration was not acceptable.

Run GLN18 (subject 15): The run was rejected for Amiodarone only, because both standard samples A (0.0 ng/mL) showed a contaminant peak of more than 25% of standard B (5.01 ng/mL) and C (10.01 ng/mL). The standard samples B and C were also rejected, and standard D (50.26 ng/mL) became the LLOQ sample. Therefore, both QC samples A (14.95 ng/mL) had to be rejected, since low concentration standards were rejected.

Runs GLN29, GLN33, and GLN35: The runs were rejected for both Amiodarone and the metabolite because of overall poor chromatography.

Run GLN37: The run was rejected because both QC samples C deviated more than 15% from the nominal concentrations for both Amiodarone and the metabolite.

Comment: The response is acceptable.

2. The analytes in plasma samples were found to be stable at 22° C for 5.0 hours. The firm was requested to clarify that the 5.0-hour was an adequate time for the short term stability study of the analytes.

Response: The firm has responded that a duration of 5.0-hour is sufficient for thawing, aliquoting, start processing, and returning the samples to the freezer.

Comment: The response is acceptable.

3. The batch size and manufacturing date of the test product were not reported.

Response: The batch size for the test product, batch #PM009 was ablets. The manufacturing date was December 09, 1996.

Comment: The response is acceptable.

4. The CV% was not reported for the dissolution testing data at each sampling time point.

Response: The firm provided the CV%s for the test and reference products. The CV%s for the reference product are higher than for the test product (Table 1).

Comment: The response is acceptable.

5. The method of assay and calculation of the dissolution testing data were requested to be submitted.

Response: The firm submitted the method of the assay on 2/12/98

and the calculations on 8/19/98.

Comment: The dissolution testing was conducted on 12 units of the test and reference products in 900 mL Sodium Acetate Buffer pH 5 with 1.0% (w/v) Sodium Lauryl Sulphate using apparatus 2 at 75 rpm (Table 1). The firm proposed specifications (Q) of in 60 minutes. The DBE recommends specifications (Q) of in 60 minutes.

The firm had previously submitted the Weight Variation for the test product. The Content Uniformity was requested by phone call from the DBE.

The firm submitted the requested data on 8/19/98. The mean Content Uniformity for the test product (batch #PM009) was with a range of (CV=1.7%, N=10), and for the reference product (batch #9961145, expiration date: 7/99) was 99.3% with a range of (CV=0.80%, N=10).

COMMENT:

The firm has also submitted a Report Amendment II for the bioequivalence study No. 960758. Laboratory tests for hematology, serum chemistry, and urinalysis were performed for subjects after the study was completed. Results of the final tests either were within the normal ranges or were not clinically significant (judged by the medical designate) for all the subjects except for subjects 14, 25, 26 and 34.

The laboratory tests were repeated for subjects 14, 25, and 26 because of a high TSH level, and for subject 34 because of a small amount of blood in urine. Results were found normal for subjects 25, 26, and 34. However, results from the repeated tests for the high TSH level for subject 14 were found clinically significant at post-study, 8 days later, and at 69 days after the period 2 dosing. This subject was sent to an endocrinologist 72 days after dosing at period 2. It was concluded that the subject had a subclinical autoimmune thyroiditis before participating in this study, which became clinically significant upon completion of the study apparently due to the iodine present in the products. The medical designate judged that no further follow up was required by The subject was sent to a family physician and will continue to be followed up by the

endocrinologist.

DEFICIENCY OF THE CURRENT SUBMISSIONS: None.

RECOMMENDATIONS:

1. The single dose bioequivalence study conducted under fasting conditions by Alphapharm PTY. LTD. on its Amiodarone Hydrochloride Tablets, 2X200 mg, batch #PM009 comparing it to Cordarone Tablets, 2X200 mg, lot #9961145 by Wyeth-Ayerst has been found acceptable.

2. The dissolution testing conducted by Alphapharm PTY. LTD. on its Amiodarone Hydrochloride Tablets, 200 mg, batch #PM009 has been found acceptable.

3. 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.

4. 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 pH 5 Sodium Acetate Buffer with 1.0% (w/v) Sodium Lauryl Sulphate at 37° C using USP 23 apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

N he drug

Farahnaz Nouravarsani

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

RD INITIALED BDAVIT BMD 9/18/98
FT INITIALED BDAVIT

Concur: _____ Date: 9/19/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

FNouravarsani/08-31-98
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Table 1: In Vitro Dissolution Testing

Drug (Generic Name): Amiodarone HCl Tablets
Dose Strength: 200 mg
ANDA: #75-188
Firm: Alphapharm PTY. LTD.
Submission Dates: August 08, 1997
February 12, 1998

I. Conditions for Dissolution Testing:

USP XXIII Basket____ Paddle X RPM 75 No. Units Tested 12

Medium: Sodium Acetate Buffer pH 5 with 1.0% Sodium Lauryl Sulphate Volume: 900 mL

Reference Drug: Cordarone Tablets, 200 mg

Assay Methodology:

Specifications (Q):

Method: FDA

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes	Test Product: Lot#PM009 Strength (mg) 200			Reference Product: Lot #9961145 Strength (mg) 200		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	60.0	.	(21.2)	36.0		(54.1)
20	77.0	.	(15.7)	57.0		(46.6)
30	83.0	.	(13.7)	66.0	.	(43.2)
40	87.0	.	(11.6)	75.0	.	(32.0)
60	91.0	.	(9.2)	84.0	.	(17.9)

Amiodarone HCl
Tablets, 200 mg
ANDA #75-188
Reviewer: F. Nouravarsani
75188SFD.897

Alphapharm PTY. LTD.
Queensland, Australia
Submission Date:
August 08, 1997

Review of a Single Dose, Fasting Bioequivalence Study and Dissolution Testing

INTRODUCTION:

Alphapharm has submitted a single dose bioequivalence study conducted under fasting conditions on its test product, Amiodarone HCl Tablets, 200 mg and the listed reference product, Cordarone, 200 mg Amiodarone HCl Tablets manufactured by Wyeth-Ayerst (NDA #18972, December 24, 1985).

Amiodarone HCl is slightly soluble in water. Cordarone is an antiarrhythmic drug, which is slowly and variably absorbed in man following its oral administration. Its bioavailability is about 50% (bioavailabilities between 35% to 65% have been seen from various studies). Peak plasma concentrations occurs at 3 to 7 hours following a single dose. Cordarone accumulates extensively in various sites, especially in liver, lung, spleen, and adipose tissue. Therefore, it has a large and variable volume of distribution of approximately 60 L/Kg. Cordarone is 96% protein bound. Its elimination is mainly by hepatic excretion into bile, and some enterohepatic recirculation may occur. The urinary excretion of Cordarone is insignificant (PDR, 1997).

The major metabolite of Cordarone in man is desethylamiodarone. It accumulates more than amiodarone in almost all tissues. The pharmacological activity of this metabolite was stated to be unknown in PDR 51 (1997). However, a study by Yabek et al suggests a comparable pharmacological activity for desethylamiodarone with amiodarone (reference 48 in: Analytical Profiles of Drug Substances, Volume 20, p 109, 1991).

The terminal mean plasma elimination half-life of amiodarone was 53 days with a range of 26 to 107 days in patients following termination of chronic oral doses of Cordarone. The mean plasma

elimination half-life of the metabolite was about 61 days (PDR, 1997).

It is suggested that Cordarone be administered with meals in divided doses for total doses of 1000 mg or higher, or when there is a gastrointestinal intolerance (PDR, 1997).

OBJECTIVES:

1. Determine the bioequivalency of a single dose of the test product, Amiodarone HCl Tablets, 2x200 mg to a single dose of the reference product, Cordarone, 2x200 mg Tablets under fasting conditions.

2. Determine the dissolution of the test and reference products.

BIOEQUIVALENCE STUDY:

Sponsor: Alphapharm PTY. LTD.
Manufacturer: Alphapharm PTY. LTD., Queensland, Australia
Clinical Facility: Clinical Research Center,
Analytical Facility:

Study Design:

A single dose of the test and reference products, each was administered randomly to healthy male volunteers in a two - way crossover study design under fasting conditions (study #960758).

Treatments:

Treatment A (test product): A single dose of Amiodarone HCl Tablets, 2x200 mg, Batch #PM 009, expiration date: December 1998.

Treatment B (reference product): A single dose of Cordarone Tablets, 2x200 mg, lot #9961145, expiration date: July 1999.

Clinical Study Dosing Dates:

Phase I: February 04, 1997
Phase II: April 08, 1997
Washout period: 9 weeks

Subjects:

Forty (40) healthy, adult, male volunteers were enrolled in the study. Seven (7) subjects (#1, 4, 17, 19, 20, 22, and 30) dropped from the study for personal reasons before period two. The range of subjects' age, weight, and height are summarized as follows:

Age: 18-35 years; Weight: 60.5-87.5 kg; Height: 164-187 cm

Housing, Fasting, and Meals:

The subjects were housed from evening before the dosing until 36 hours after the dose at each period. 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:

A total of twenty (20) blood samples, 10 mL each, were collected for each phase at pre-dose, and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, 24.0, 36.0, 48.0, 72.0, 96.0, 144.0, 240.0, 336.0, 504.0, and 672.0 hours post-dose.

Vital Signs:

Sitting blood pressure and heart rate were determined at pre-dose, and approximately at 1, 2, 4, 6, 8, 12, and 24 hours post-dose.

Safety Monitoring:

A 12-lead EKG was performed at pre-dose, and approximately at 3, 5, 10, and 24 hours after the dose.

Analytical Procedures:

The plasma samples were analyzed for Amiodarone and Desethylamiodarone using a
with detection assay method. The analytical method was developed and validated at Inc.
A total of 1316 samples were assayed. Four samples were not received.

Lower Limit of Quantitation:

Amiodarone: 5.01 ng/mL
Desethylamiodarone: 5.02 ng/mL

Linearity:

Linear regression analysis, weighting factor: 1/concentration

Specificity:

There were no interferences from the analytes and the internal standard.

Internal Standard: Clomiphene Citrate

Accuracy:

Amiodarone
(a) from the standard samples, concentration range of
ng/mL, Interday:

(b) from the quality control samples, concentration range of
.74 ng/mL, Interday:

Desethylamiodarone:
(a) from the standard samples, concentration range of
/mL, Interday:

(b) from the quality control samples, concentration range of
ng/mL, Interday:

Precision, CV%:

Amiodarone
(a) from the standard samples, concentration range of
nL, Interday:

(b) from the quality control samples, concentration range of
g/mL, Interday:

Desethylamiodarone:
(a) from the standard samples, concentration range of
ıg/mL, Interday:

(b) from the quality control samples, concentration range of
ıg/mL, Interday:

Absolute Recovery in Human Plasma:

Amiodarone: 78.0% at 19.98 ng/mL, N=10
83.0% at 534.72 ng/mL, N=14
91.8% at 1066.73 ng/mL, N=10

Desethylamiodarone: 69.5% at 19.98 ng/mL, N=10
85.4% at 534.71 ng/mL, N=14
99.2% at 1066.73 ng/mL, N=10

Internal Standard: 87.3%

Stability Studies:

Frozen Long Term Stability:

The frozen plasma stability study period, 195 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 134 days.

Short Term (Benchtop) Stability:

The analytes in plasma samples were stable at 22° C for 5.0 hours.

Freeze-Thaw Stability:

The analytes in plasma samples were stable after three freeze-thaw cycles.

Autosampler Stability:

The analytes were stable at 22° C for 18.4 hours. The extended autosampler stability samples of both Amiodarone and its metabolite were found stable at 22° C for 88 hours.

Statistical Analysis:

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

Results:

Amiodarone:

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

The mean AUC(0-T) obtained for the test product Amiodarone, 9407.9 hr*ng/mL is comparable with the one obtained from the reference product, 10221.5 hr*ng/mL.

The mean value of 10448.4 hr*ng/mL obtained for the test product AUC(0-Inf) is comparable with the one obtained for the reference product, 11517.1 hr*ng/mL. The AUC(0-Inf) for Amiodarone was not calculated for 1 subject (#40) for the test product, and for 2 subjects (#18 and #23) for the reference product.

The mean ratio of AUC(0-T) to AUC(0-Inf) was 89.9% (range:

for the test product, and 89.3% (range:) for the reference product (Table 3).

Mean C(Max) value of 366.20 ng/mL obtained for the test product is also comparable with mean C(Max) value of 383.5 ng/mL obtained for the reference product.

Mean T(Max) value was 6.1 hours (range: ours) for the test product, and 6.1 hours (range: hours) for the reference product.

Mean T(1/2) value was 119.1 hours (range: ours) for the test product, and 120.4 hours (range: ours) for the reference product.

The 90% confidence intervals based on Least-Squares Means obtained for Amiodarone parameters (ln-transformed) of AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range of able 2). There is a sequence effect ($p<0.1$) for both un-transformed and ln-transformed C(Max). The intrasubject CV% for ln-transformed parameters of AUC(0-T), AUC(0-Inf), and C(Max) were 28.7%, 29.4%, and 32.8%, respectively.

The mean (CV%) and range for ratio of the test product to the reference product for AUC(0-T) were 104% (39%) and respectively.

The mean (CV%) and range for ratio of the test product to the reference product for AUC(0-Inf) were 102% (44%) and respectively.

The mean (CV%) and range for ratio of the test product to the reference product for C(Max) were 107% (47%) and respectively.

Desethylamiodarone:

Mean plasma concentrations of Desethylamiodarone obtained from the test and reference products are summarized in Table 4. Plots of the mean plasma concentrations of Desethylamiodarone versus time for the test and reference products, ln-transformed and un-transformed, respectively, are shown in Figures 3 and 4. The means of the pharmacokinetic parameters for Desethylamiodarone obtained

from the test and reference products are compared in Table 5.

The mean AUC(0-T) obtained for the test product, 12547.1 hr*ng/mL is comparable with the one obtained from the reference product, 12848.8 hr*ng/mL.

Mean value of 15297.4 hr*ng/mL obtained for the test product AUC(0-Inf) is comparable with the one obtained for the reference product, 15957.3 hr*ng/mL. The AUC(0-Inf) could not be calculated for 1 subject (#27) for the reference product.

The mean ratio of AUC(0-T) to AUC(0-Inf) was 81.4% (range:) for the test product, and 82.4% (range:) for the reference product (Table 6).

Mean C(Max) value of 64.4 ng/mL obtained for the test product is also comparable with the mean C(Max) value of 66.9 ng/mL obtained for the reference product.

Mean T(Max) value was 18.0 hours (range: 6-36 hours) for the test product, and 18.2 hours (range: 5-36 hours) for the reference product.

Mean T(1/2) value was 248.3 hours (range: 128-454 hours) for the test product, and 247.7 hours (range: 141-592 hours) for the reference product.

The 90% confidence intervals based on Least-Squares Means obtained for parameters (ln-transformed) of AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range of 80 - 125% (Table 5). There is sequence effect for AUC(0-T) and C(Max), both un-transformed and ln-transformed ($p<0.1$). The intrasubject CV% for ln-transformed parameters of AUC(0-T), AUC(0-Inf), and C(Max) were 19.3%, 20.6%, and 18.8%, respectively.

The mean (CV%) and range for ratio of the test product to the reference product for AUC(0-T) were 98% (27%) and 54%-162%, respectively.

The mean (CV%) and range for ratio of the test product to the reference product for AUC(0-Inf) were 100% (27%) and respectively.

The mean (CV%) and range for ratio of the test product to the reference product for C(Max) were 99% (29%) and 58%-189%, respectively.

Medical Events:

The following medical events were related to the products.

Event	Product	Subject	Related to Drug
headache	test	6	possible
	test	25	probable
	test	36	possible
	test	37	possible
	ref.	6	possible
	ref.	25	possible
	ref.	36	possible
nausea	test	8	possible
	test	35	possible
	ref.	25	probable
feels dizzy	test	18	possible
	ref.	25	probable
	ref.	36	possible
irregular pulse	test	24	possible
hard to breathe	test	25	possible
cough	test	25	possible
palpitation	ref.	23	possible
bad taste in mouth	ref.	36	probable

Subject #25 vomited ("Subject complained of upset stomach and insisted on inducing vomiting") at 14.9 hour and 1.2 day after the treatment A at period 1. The probability of this medical event was reported to be "unlikely" to be related to the drug product. The T(Max) for the subject was 6.0 hours for the treatment A.

In-Vitro Studies:

Dissolution Testing:

The firm has stated that dissolution method and specifications were those specified by the Division of Bioequivalence. The dissolution testings were conducted on 12 units of the test and reference products in 900 mL Sodium Acetate Buffer pH 5 with 1% (w/v) Sodium Lauryl Sulphate using apparatus 2 at 75 rpm (Table 7). The specifications (Q) are NLT .

Assay Potency:

Assay potencies of 97.6% and 97.9% of the label claimed were obtained for the test and reference products, respectively. Formulations of the test and reference products are compared in Table 8.

Content Uniformity:

Mean (CV%, N) content uniformity of 97.5% (0.76%, N=10) was obtained for the test product.

COMMENTS:

1. Batch #PM 009, test product, and lot #9961145, reference product, were used for both, the bioequivalence study and the dissolution testing.

2. More than one peak are observed for both Amiodarone and Desethylamiodarone for some of the subjects. The presence of multiple peaks is apparently due to the enterohepatic recirculation of Amiodarone.

3. The AUC(0-Inf) was not calculated for Amiodarone for subject #40 (test product), and for subjects #18 and #23 (reference product) because of difficulty to calculate the K(Elm). The AUC(0-Inf) was not calculated for Desethylamiodarone for subject #27 (reference product).

4. The following four plasma samples were not obtained, and were set as missing values:
subject #6, period 2, reference product, at 504 hours;

subject #39, period 1, test product, at 504 hours; and
subject #39, period 2, reference product, at 48 and 336 hours.

5. The pre-dose plasma concentration of desethylamiodarone for subject #13, period 2, test product was 5.28 ng/mL. This value was not confirmed, since the sample was not reassayed. The lower limit of quantitation was 5.02 ng/mL.

The pre-dose plasma concentrations of desethylamiodarone for subjects #8 and #33, period 2 were 9.28 ng/mL and 6.09 ng/mL, respectively. The levels of the repeated assay for these samples were less than the lower limit of quantitation (5.02 ng/mL).

6. There was a sequence effect ($p<0.1$) for Amiodarone un-transformed and ln-transformed C(Max), and for Desethylamiodarone un-transformed and ln-transformed AUC(0-t) and C(Max).

The firm has stated that the sequence effect is not likely to be result of the non-zero plasma levels at pre-dose for subjects #8, #13, and #33 in period 2, since the sequence effect was still observed by excluding these subjects. Furthermore, subject #8 was not in the same sequence as the subjects #13 and #33. Therefore, this effect is not due to an unequal carryover of the drug, but may be because of random differences in subjects on sequence AB and those on sequence BA.

DEFICIENCIES:

1. The firm has stated that "results from rejected batches, if any, are not included in the report".

The rejected runs, if any, and the reason(s) for rejecting should be submitted by the firm.

2. The analytes in plasma samples were found to be stable at 22° C for 5.0 hours. The firm should clarify that the 5.0 hours was an adequate time for the short term stability study of the analytes.

3. The batch size and manufacturing date of the test product were not reported.

4. The CV% was not reported for dissolution testing data at each sampling time point.

5. The method of assay and calculation of the dissolution testing data should be submitted.

RECOMMENDATIONS:

1. The single dose bioequivalence study conducted under fasting conditions by Alphapharm PTY. LTD. on its Amiodarone Hydrochloride Tablets, 2X200 mg, batch #PM009 comparing it to Cordarone Tablets, 2X200 mg, lot #9961145 by Wyeth-Ayerst has been found incomplete by the Division of Bioequivalence.

2. The dissolution testing conducted by Alphapharm PTY. LTD. on its Amiodarone Hydrochloride Tablets, 200 mg, batch #PM009 has been found incomplete.

The firm should be informed of the deficiencies and recommendations.

/S/

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

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Concur: /S/ Date: 1/8/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

FNouravarsani/01-08-98/75188SFD.897

Table 1

Arithmetic Mean (CV%) Plasma Concentrations of Amiodarone (ng/mL), N=33:

Time, hr	Test Product	Ref. Product
0.0	0.00 (---)	0.00 (---)
1.0	46.75 (120)	57.13 (107)
2.0	136.65 (94)	145.37 (74)
3.0	212.43 (82)	218.59 (49)
4.0	238.55 (51)	253.85 (62)
5.0	307.28 (41)	343.08 (71)
6.0	337.61 (38)	362.60 (57)
7.0	322.98 (41)	347.67 (59)
8.0	297.55 (44)	317.62 (64)
12.0	209.49 (47)	219.08 (63)
24.0	93.16 (51)	96.21 (64)
36.0	74.69 (62)	81.05 (86)
48.0	40.45 (47)	47.05 (74)a
72.0	23.99 (45)	24.63 (62)
96.0	16.21 (43)	16.63 (67)
144.0	10.44 (47)	12.00 (73)
240.0	5.33 (77)	6.20 (106)
336.0	1.97 (156)	3.28 (129)b
504.0	1.32 (219)a	1.37 (221)a
672.0	0.73 (277)	0.84 (333)

a: N = 32
b: N = 31

Table 2

Arithmetic Mean (CV%), Ratio, and 90% CI for Amiodarone Pharmacokinetic Parameters Obtained from the Test and Reference Products, N=33:

Parameters	Test Product	Ref. Product	Ratio*	90% CI**
AUC(0-T) hr*ng/mL	9407.9(50)	10221.5(72)	96.8%	86.1-108.9
AUC(0-Inf) hr*ng/mL	10448.4(51)a	11517.1(73)b	94.5%	83.2-107.2
C(Max) ng/mL	366.2(46)	383.5(61)	97.2%	85.1-111.1
T(Max) hr	6.1(16)	6.1(18)		
K(Elm) 1/hr	0.0101(73)a	0.0107(96)b		
T(1/2) hr	119.1(83)a	120.4(79)b		

* = using geometric means (least-squares)
** = using ln-transformed data
a: N = 32
b: N = 31

Table 3: Amiodarone AUC(0-T)/AUC(0-Inf) Percentage:

Subject	Test	Reference
02		
03		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
18		
21		
23		
24		
25		
26		
27		
28		
29		
31		
32		
33		
34		
35		
36		
37		
38		
39		
40		
Mean%	89.94	89.25
CV%	6.6	6.2
Range%	64.9-96.0	74.1-98.6
N	32	31

Table 4

Arithmetic Mean (CV%) Plasma Concentrations of Desethylamiodarone (ng/mL), N=33:

Time, hr	Test Product	Ref. Product
0.0	0.16 (575)	0.00 (---)
1.0	1.03 (397)a	0.77 (266)c
2.0	6.65 (103)a	7.40 (93)a
3.0	16.77 (61)b	16.40 (63)c
4.0	23.49 (46)a	25.06 (45)b
5.0	39.63 (36)	44.90 (35)a
6.0	47.62 (33)	49.68 (32)
7.0	52.46 (36)	52.50 (35)
8.0	54.11 (30)	55.85 (30)
12.0	61.34 (29)	64.06 (28)
24.0	54.38 (29)	54.30 (22)a
36.0	54.77 (33)	56.81 (22)
48.0	44.87 (37)	44.98 (27)a
72.0	38.31 (39)	37.14 (28)
96.0	34.48 (35)	34.26 (30)
144.0	28.00 (35)	28.58 (34)
240.0	19.40 (36)	20.73 (21)
336.0	14.33 (32)	15.47 (22)a
504.0	8.92 (60)a	8.82 (43)a
672.0	4.78 (85)	4.69 (93)

a: N = 32
b: N = 30
c: N = 31

Table 5

Arithmetic Mean (CV%), Ratio, and 90% CI for Desethylamiodarone Pharmacokinetic Parameters Obtained from the Test and Reference Products, N=33:

Parameters	Test Product	Ref. Product	Ratio*	90% CI**
AUC(0-T) hr*ng/mL	12547.1(36)	12848.8(24)	93.8%	86.6-101.6
AUC(0-Inf) hr*ng/mL	15297.4(33)	15957.3(24)a	95.4%	87.5-104.1
C(Max) ng/mL	64.4(28)	66.9(26)	95.2%	88.1-103.0
T(Max) hr	18.0(58)	18.2(64)		
K(Elm) 1/hr	0.0031(31)	0.0031(28)a		
T(1/2) hr	248.3(33)	247.7(35)a		

* = using geometric means (least-squares)
** = using ln-transformed data
a: N = 32

Table 6: Desethylamiodarone AUC(0-T)/AUC(0-Inf) Percentage:

Subject	Test	Reference
02		
03		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
18		
21		
23		
24		
25		
26		
27		
28		
29		
31		
32		
33		
34		
35		
36		
37		
38		
39		
40		
Mean%	81.44	82.43
CV%	9.9	10.4
Range%	57.9-92.4	52.8-91.9
N	33	32

Table 7: In Vitro Dissolution Testing

Drug (Generic Name): Amiodarone HCl Tablets
Dose Strength: 200 mg
ANDA: #75-188
Firm: Alphapharm PTY. LTD.
Submission Date: August 08, 1997

I. Conditions for Dissolution Testing:

USP XXIII Basket____ Paddle X RPM 75 No. Units Tested 12

Medium: Sodium Acetate Buffer pH 5 with 1.0% Sodium Lauryl Sulphate Volume: 900 mL

Reference Drug: Cordarone Tablets, 200 mg

Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes	Test Product: Lot#PM009 Strength (mg) 200			Reference Product: Lot #9961145 Strength (mg) 200		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	60.0	-	(....)	36.0	-	(....)
20	77.0	-	(....)	57.0	-	(....)
30	83.0	-	(....)	66.0	-	(....)
40	87.0	-	(....)	75.0	-	(....)
60	91.0	-	(....)	84.0	-	(....)

Table 8: Formulations Comparison of the Test and Reference products, mg/Tablet:

Ingredients	Test,mg	Ref., mg (a)
e HCl		
e		

a:
b:
c:
d:
X:

Figure 1

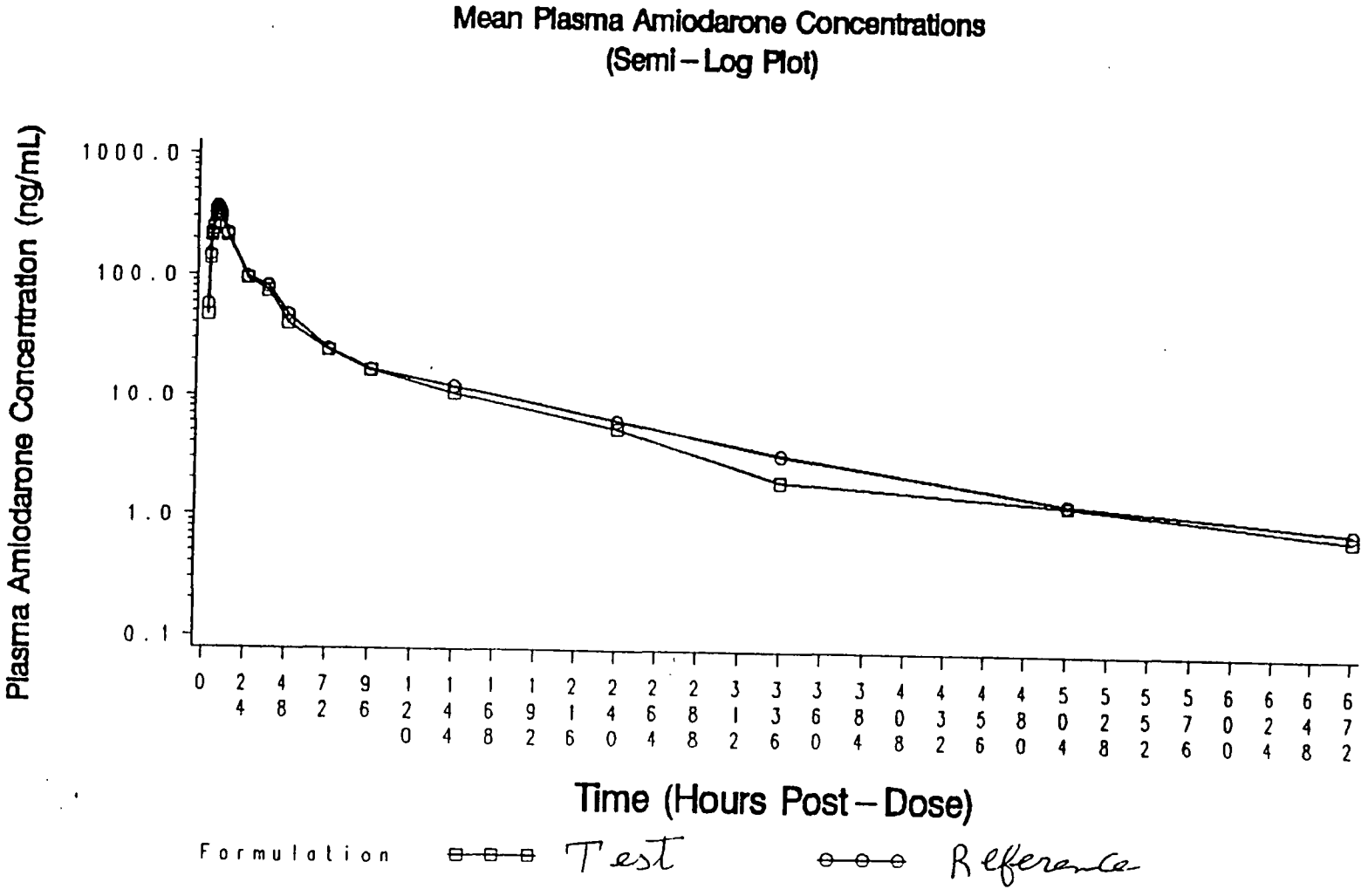

Mean Plasma Amiodarone Concentrations
(Semi – Log Plot)
Plasma Amiodarone Concentration (ng/mL)
1000.0
100.0
10.0
1.0
0.1
0 24 48 72 96 120 144 168 192 216 240 264 288 312 336 360 384 408 432 456 480 504 528 552 576 600 624 648 672
Time (Hours Post – Dose)
Formulation Test Reference

Figure 2

Mean Plasma Amiodarone Concentrations (Linear Plot)

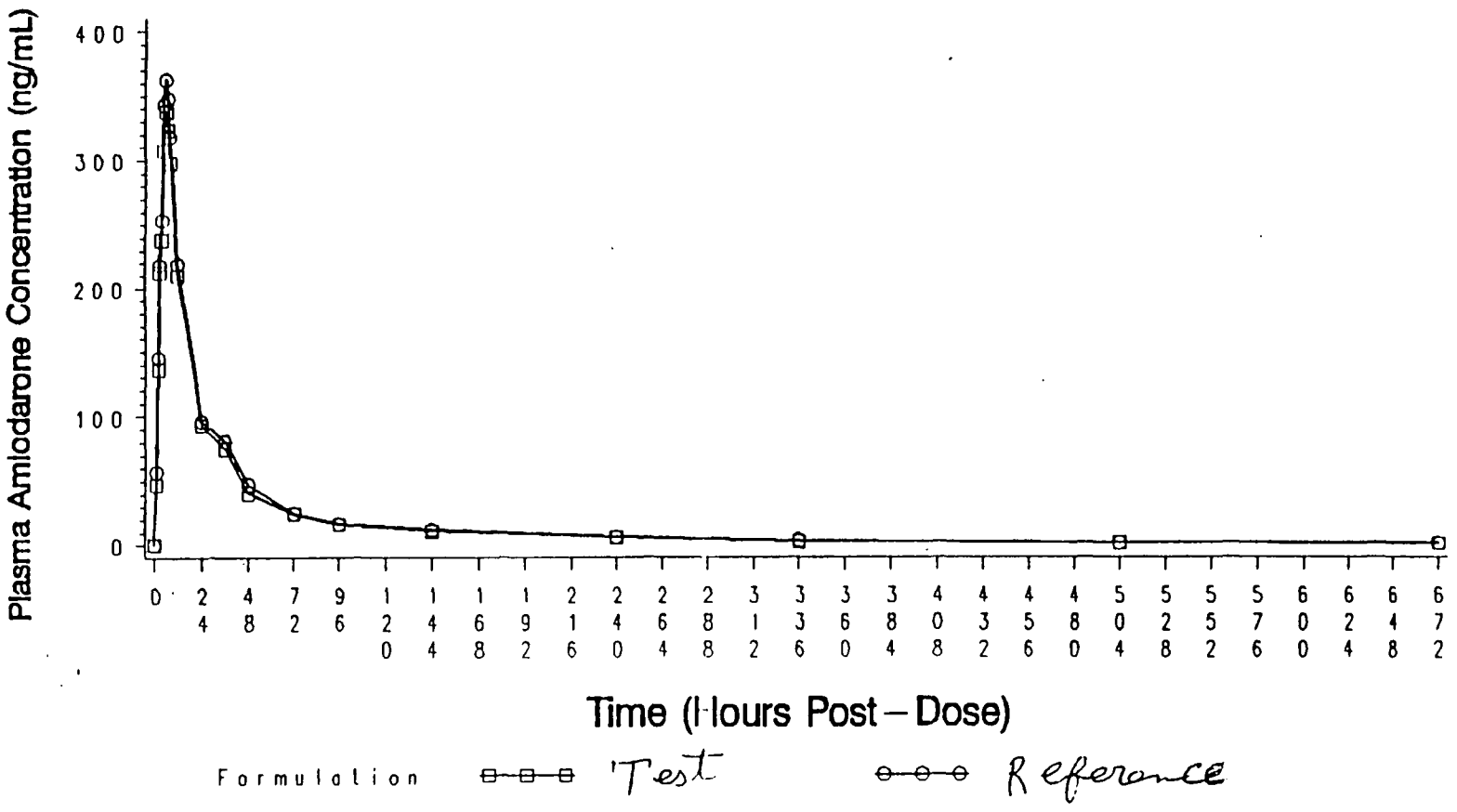


Figure 3

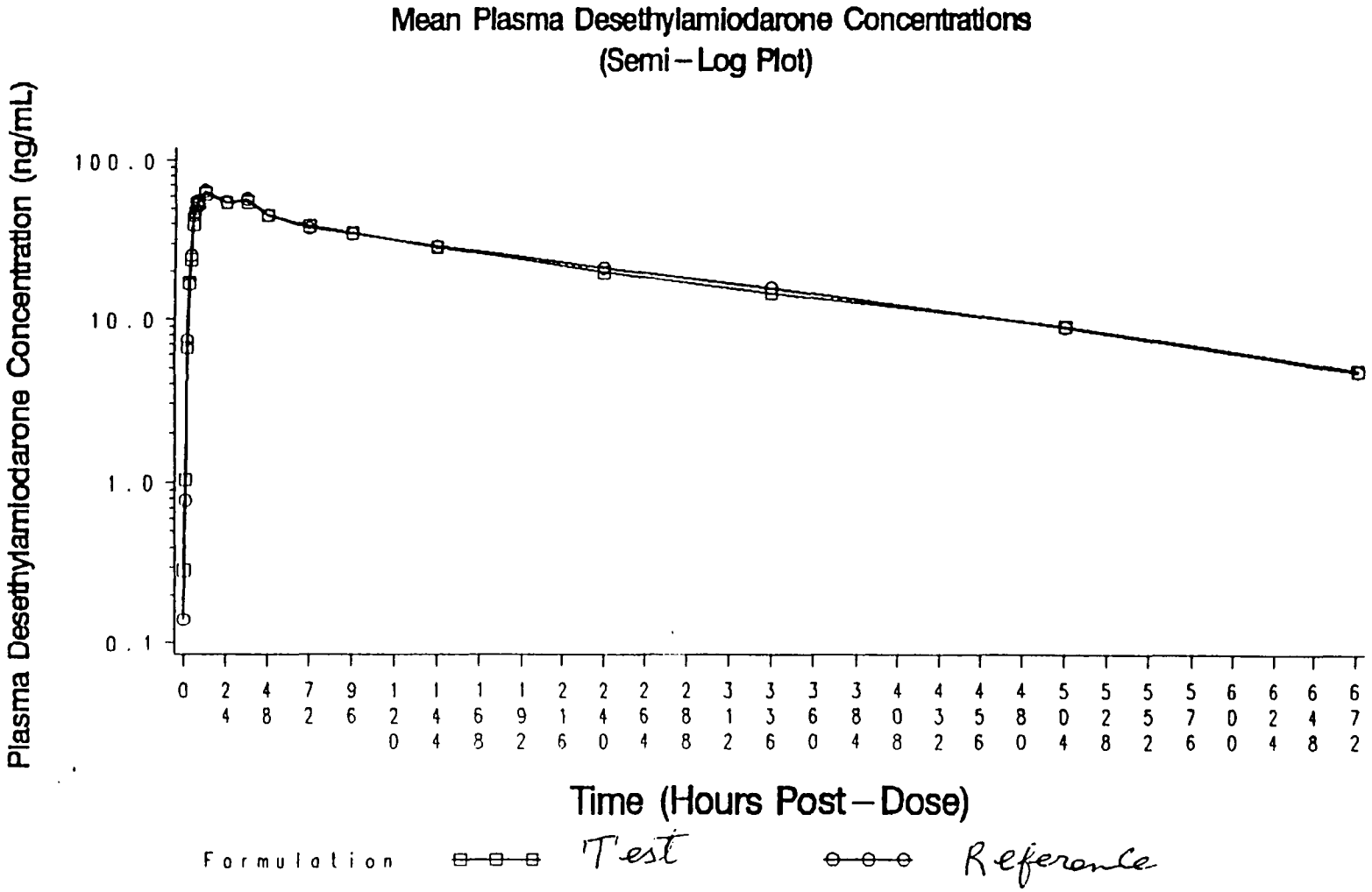
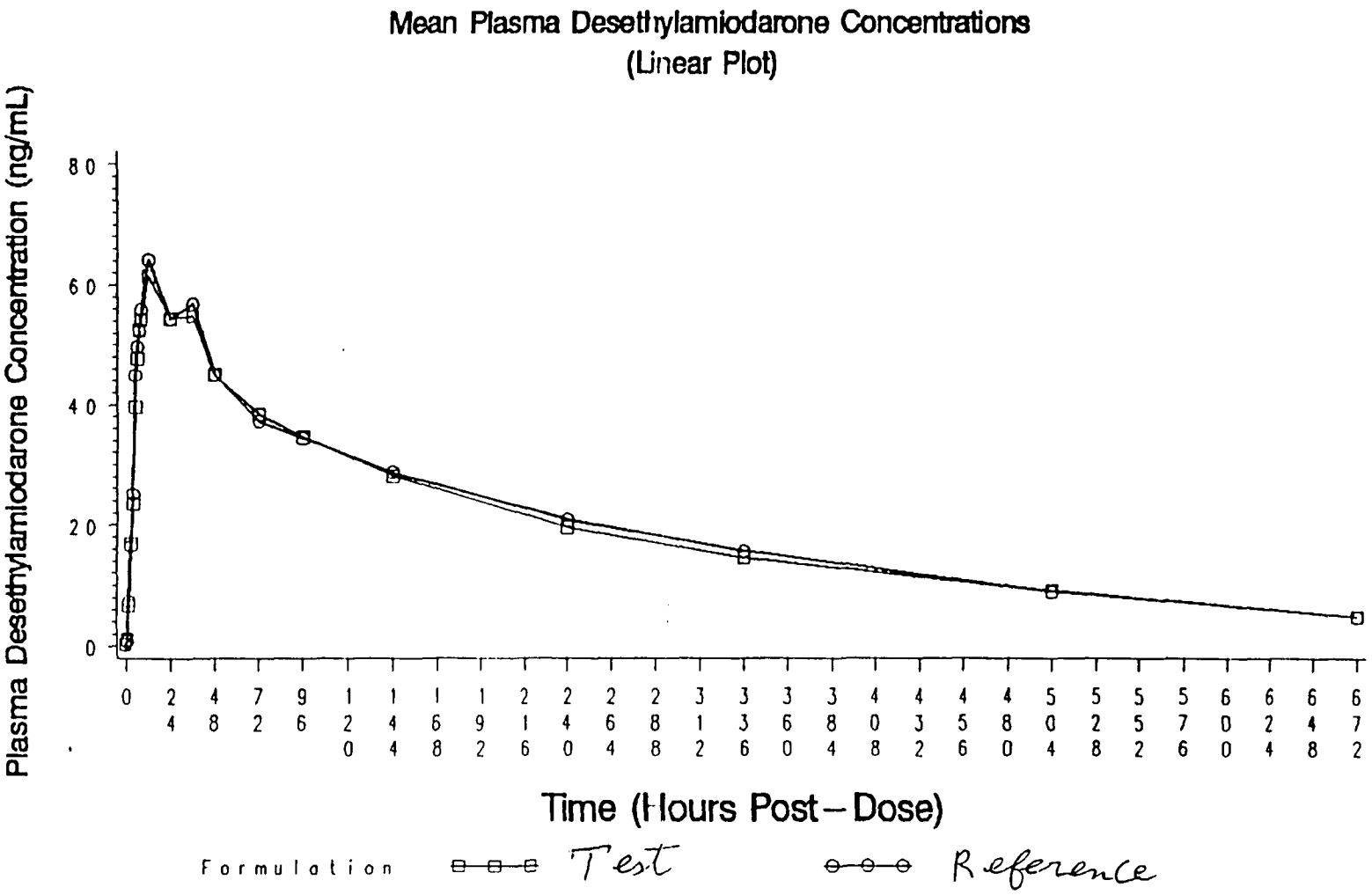

Mean Plasma Desethylamiodarone Concentrations
(Semi – Log Plot)
Plasma Desethylamiodarone Concentration (ng/mL)
100.0
10.0
1.0
0.1
0 24 48 72 96 120 144 168 192 216 240 264 288 312 336 360 384 408 432 456 480 504 528 552 576 600 624 648 672
Time (Hours Post – Dose)
Formulation
Test
Reference

Figure 4


Mean Plasma Desethylamiodarone Concentrations
(Linear Plot)
Plasma Desethylamiodarone Concentration (ng/mL)
80
60
40
20
0
0 24 48 72 96 120 144 168 192 216 240 264 288 312 336 360 384 408 432 456 480 504 528 552 576 600 624 648 672
Time (Hours Post-Dose)
Formulation Test Reference