CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74914

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-914 SPONSOR: copley pharmaceutical
DRUG: Acyclovir
DOSAGE FORM: Capsules
STRENGTH(s): 200 mg
TYPE OF STUDY: Single/~~Multiple~~ Fasting/Fed
STUDY SITE: PRACS

STUDY SUMMARY: The firm's in vivo bioequivalence studies under fasting and nonfasting conditions are acceptable. The 90% CIs for Ln AUCTLac, Ln AUCinf and Cmax are within the acceptable range of 80-125% under fasting conditions. The ratios of the test mean to the reference mean are within the acceptable range 0.8-1.2 for the above parameters.

DISSOLUTION: Dissolution testing is acceptable.

PRIMARY REVIEWER: Malcolm H. Marcy BRANCH: III

INITIAL: MHM DATE: 8/8/97

BRANCH CHIEF: BRANCH:

INITIAL: DATE:

DIRECTOR
DIVISION OF BIOEQUIVALENCE

for

INITIAL: /S/ DATE: 11/24/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

SEP 14 1997

Acyclovir
200 mg Capsule
ANDA 74-914
Reviewer: Moheb H. Makary
WP 74914SD.297

Copley Pharmaceutical Inc.
Canton, MA
Submission Date:
February 14, 1997

Review of An Amendment to Bioequivalence Studies, and Dissolution Data

I. Objective:

The firm has replied to the reviewer's comment made in the review of the June 18, 1996 submission (bioequivalence studies on Acyclovir 200 mg Capsule and dissolution data).

II. Comment

The firm was advised to provide dissolution testing data using the method in FDA /PF Volume 22, Number 4, July-August, 1996:

Medium: 900 mL of water
Apparatus I (basket) at 100 rpm

The firm submitted the dissolution testing results using the above method (Table I).

Reply to Comment

The firm's response to the comment is acceptable.

III. Recommendations:

1. The bioequivalence studies conducted by Copley Pharmaceutical, Inc., under fasting and nonfasting conditions on its Acyclovir, 200 mg Capsule, lot #299Z01, comparing it to Glaxo-Wellcome's Zovirax® 200 mg Capsule have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Copley's Acyclovir Capsule, 200 mg is bioequivalent to the reference product, Zovirax®, 200 mg Capsule, manufactured by Glaxo-Wellcome.

2. The dissolution testing conducting by Copley Pharmaceutical, Inc., on its Acyclovir, 200 mg Capsules, lot #299Z01, is acceptable.

3. 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 using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

NLT ( ) % of labeled amount of the drug in the dosage form is dissolved in 30 minutes

The firm should be informed of the above recommendations.

/S/

Moheb H Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 8/14/97

Concur: /S/ 9/14/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

MMakary/8-8-97 wp 74914SD.597
cc: ANDA #74-914, original, HFD-650 (Director), HFD-658 (Makary), Drug File, Division File.

Table I. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Capsules
Dose Strength: 200 mg
ANDA No.: 74-914
Firm: Copley
Submission Date: May 2, 1997
File Name: 74914SD.597

I. Conditions for Dissolution Testing:

USP 23 Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 mL of Water
Specifications: NLT % in 30 minutes
Reference Drug: Zovirax
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 299Z01 Strength(mg) 200			Reference Product Lot # 4U1356 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	55.8		22.4	66.5		14.7
20	93.4		7.1	95.2		5.7
30	97.1		3.6	99.6		2.7
45	99.5		2.2	100.8		2.0

Acyclovir
200 mg Capsule
ANDA 74-914
Reviewer: Moheb H. Makary
WP 74914SD.696

SEP 13 1996

Copley Pharmaceutical Inc.
Canton, MA
Submission Date:
June 18, 1996

Review of Two Bioequivalence Studies and Dissolution Data

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its Acyclovir 200 mg Capsules and dissolution data to compare the test product relative to Zovirax^{R} (Glaxo-Wellcome) 200 mg capsules for review. The formulation for the drug product Acyclovir 200 mg Capsules was also submitted.

II. Background:

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside with antiviral activity against human herpes viruses, including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VCV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). The viral inhibitory activity is highly selective, involving preferential uptake into virus-infected cells and requiring a virus-specific thymidine kinase for conversion to the monophosphate. Subsequent conversion to the triphosphate results in irreversible binding to DNA polymerase and termination of DNA replication. Acyclovir capsules, tablets and suspension are indicated for the treatment of initial episodes and management of recurrent episodes of genital herpes in certain patients and for the acute treatment of herpes zoster and chicken pox.

Acyclovir is marketed as Zovirax (Glaxo-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 mL (NDA #19-909, 12/22/89).

Pharmacokinetics

The oral absorption of acyclovir is slow, variable, and incomplete, with absolute bioavailability estimated as (15-30)% from different studies involving both normals and patients. Reported values for C_{max} and T_{max} in healthy subjects after a 200 mg capsule were 0.3 ± 0.1 mg/L and 1.5-2.5 hours, respectively. Several studies in healthy volunteers have demonstrated dose-dependent absorption: (1) fraction of the dose recovered unchanged in the urine decreased over the dosing range of (100-600) mg (13.2% of a 100 mg dose; (12.1)%, 200 mg; (7.4)%, 400 mg; (6)%, 600 mg dose); (2) mean C_{MAX} was 0.58 mg/L after a single 600 mg dose and 0.50 mg/L after a single 200 mg dose; (3) mean AUC after a 600 mg dose given as divided doses every four hours, was about three times higher than after a single

600 mg dose; and (4) mean AUC from a 400 mg dose given as a duodenal infusion was about 1.7 times that from tablets, which suggested capacity-limited absorption. However, the results of one multiple dose study (200 mg q4h vs. 3 X 200 mg q4h) in immunocompromised patients suggested that net absorption of acyclovir is nearly proportional to dose in the 200-600 mg dose range.

Plasma elimination of acyclovir is biphasic with a beta phase half-life of 2-3 hours. Renal excretion is the major route of elimination with (45-79)% of a dose recovered unchanged in the urine. After an intravenous infusion of a ^{14}C tracer dose in patients, 71-99% of the dose was recovered in the urine. There is only one significant, inactive metabolite, 9-carboxymethoxymethyl guanine (CMMG), which accounts for 8-14% of a dose.

III. Project/Protocol #B-02015 For Single-dose Fasting Bioequivalence Study:

Study site:

Analytical site:

Study design: A randomized, single-dose, open-label, 2-way crossover bioequivalence study under fasting conditions.

Study dates: Period I, September 17, 1995
Period II, September 30, 1995

Subjects: Forty (40) male volunteers were enrolled in the study. All met the selection criteria described in the protocol. They were judged to be healthy based on medical history, physical examination and clinical laboratory tests within 14 days prior to period 1 dosing. All subjects were within 18 to 40 years of age and the weight range was not more than ± 10% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table.

Exclusion criteria: a. Volunteers with a recent history of drug or alcohol addiction or abuse.
b. Volunteers with the presence of a clinically significant disorder involving the cardiovascular, respiratory, renal,

gastrointestinal, immunologic, hematologic, endocrine, or neurologic system or psychiatric disease.
c. Volunteers demonstrating a positive hepatitis B surface antigen screen HIV 1 & 2 antibody screen.
d. Volunteers with a history of allergic response to acyclovir or related drugs.
e. Volunteers who report receiving any investigational drug within 30 days prior to period I.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: A. 1x200 mg Acyclovir Capsules (Copley), lot #299Z01, lot size, capsules, Content uniformity and potency are 98.7% (%CV=2.0) and 99.9%, respectively.

Reference product: B. 1x200 mg Zovirax® Capsules (Glaxo-Wellcome), lot #4U1356, Exp. 10/97. Content uniformity and potency are 98.5% (%CV=1.6) and 97.8%, respectively.

Food and fluid intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. Water was permitted ad lib. until 1 hour before dosing and 2 hours after dosing. All subjects consumed 240 mL of water two hours after dosing.

Blood collection: Blood samples (10 mL) were drawn into Vacutainers prior to drug administration. Similarly, 1x10 mL samples were drawn at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 14 and 16 hours. All blood samples were drawn at 1 minute intervals. Blood samples were centrifuged at 2400 RPM for 15 minutes. Plasma samples were stored at -20°C until shipment.

Washout period: Thirteen days.

Assay Methodology:

Statistical Analysis:

AUCTLQC, AUCinf, Cmax, Kel, T1/2 and concentrations at each sampling time point were determined for acyclovir. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for LnAUCTLQC, LnAUCinf and LnCmax.

IV. In Vivo Results:

Forty (40) subjects enrolled and thirty-nine (39) subjects

completed the study. Subjects #40 was dropped prior to period II dosing secondary to left knee bursitis which required antibiotic therapy. Twenty-seven adverse events were reported in fourteen of forty subjects dosed over the course of the study. Of the twenty-seven reported adverse events, one (headache) was possibly related to study drug. In the opinion of the investigator, the other twenty-six adverse events were either remotely related to or unrelated to study drug. None of the adverse events were considered serious. There were no clinically significant changes in the laboratory measurements over the course of the study which could be reasonably associated with the formulations under investigation. In general, the clinical portion of the study was completed without any significant consequence attributable to the investigational drug. There were eight minor deviations from the volunteer instructions of no nonprescription medications within seven days of period I dosing. In general, all blood collections were successfully completed as per protocol design.

The plasma concentrations and pharmacokinetic parameters for acyclovir are summarized below in Table I.

Table I

Mean Plasma Acyclovir Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 Acyclovir Capsule under Fasting Conditions
(N=39)

Time hr	Treatment A Copley-Test Lot #299Z01 ng/mL(CV%)	Treatment B Glaxo-Wellcome Lot #4U1356 ng/mL(CV%)
0	0	0
0.25	2.37 (367)	1.12 (436)
0.50	105.81 (85.4)	90.48 (76.0)
0.75	244.19 (51.9)	218.27 (58.1)
1.00	316.47 (41.3)	275.48 (49.9)
1.25	345.76 (38.8)	306.17 (46.7)
1.50	346.60 (39.5)	325.80 (42.4)
1.75	351.43 (41.6)	344.28 (42.6)
2.00	342.64 (37.5)	342.39 (37.4)
2.50	323.05 (35.2)	332.64 (37.0)
3.00	303.26 (38.0)	309.00 (41.2)
4.00	230.43 (38.4)	240.10 (45.4)
6.00	137.48 (36.6)	140.55 (45.9)
8.00	84.90 (33.6)	86.78 (41.6)
10.00	52.43 (32.2)	53.89 (36.4)
12.00	34.73 (37.4)	34.91 (35.4)

14.00	22.18 (58.9)	22.82 (60.7)
16.00	12.84 (96.4)	11.34 (119)

AUCTLQC(ng.hr/mL)	1955.73 (30.5)	1952.45 (35.6)
AUCinf (ng.hr/mL)	2074.62 (28.8)	2078.70 (33.4)
Cmax (ng/mL)	423.87 (33.7)	411.15 (33.9)
Tmax (hr)	1.57	1.72
Kel(1/hr)	0.21	0.21
T1/2(hr)	3.36	3.47

	90% CI
LnAUCTLQC	92.0-111.6%
LnAUCinf	92.1-110.2%
LnCmax	93.2-114.5%

1. For Acyclovir, the least squares means for AUCTLQC, Cmax and AUCinf values were 0.02%, 2.9% higher and 0.3% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The Acyclovir mean plasma levels peaked at 1.75 hours for both the test and the reference products following their administration under fasting conditions.

3. It should be noted that subject #24, period I (test product treatment) experienced two mild episodes of vomiting at 15 and 19 hours post dosing. These episodes should have no impact on the integrity of the outcome of the study.

V. Study #B-02025 For Single-dose Post Prandial Bioequivalence Study of Acyclovir 200 mg Capsules

The objective of this study was to evaluate the effect of food on the rate and extent of absorption of a single dose of Acyclovir 200 mg Capsules (Copley) relative to Zovirax® 200 mg Capsules (Glaxo-Wellcome)

Study site:

Analytical site:

Statistical Analysis:

Study design: Single-dose, three-way crossover, post-prandial bioequivalence study.

Study dates: Period I, January 13, 1996
Period II, January 20, 1996
Period III, January 27, 1996

Subjects: Eighteen (18) healthy male volunteers were enrolled in the study. All met the selection criteria described in the protocol. All eighteen subjects completed the entire clinical portion of the study.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: A. 1x200 mg Acyclovir Capsule (Copley), lot #299Z01, administered following an overnight fast.
B. 1x200 mg Acyclovir Capsule (Copley), lot #299Z01, administered within 30 minutes of a high fat breakfast preceded by an overnight fast.

Reference product: B. 1x200 mg Zovirax^{R} Capsules (Glaxo-Wellcome), lot #4U1356, administered within 30 minutes of high fat breakfast preceded by an overnight fast.

Food and fluid intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. No fluid except that given with the standardized breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice) and with drug administration was allowed from 1 hour prior to dose administration until 2 hours after dosing. All subjects consumed 240 mL of water two hours after dosing. Four hours after dose, water was allowed ad lib, if requested, but was generally controlled during confinement and limited to approximately 2160 mL from the time of dosing until release from the study site.

Blood collection: Same as Study #B-02015 above.

Washout period: One week.

Assay Methodology:

Statistical Analysis

Cmax for acyclovir was determined by establishing the peak concentration for each subject. The areas under the plasma acyclovir concentration versus time curves (AUCs) were calculated by using the linear trapezoidal rule.

VI. In Vivo Results:

Eighteen (18) subjects enrolled in the study. The study was successfully completed in all 18 subjects enrollment.
Statistical analysis was performed on all 18 subjects who completed the study.
Twenty adverse events were reported in eleven of the eighteen subjects dosed and included the following events: headache (10), abdominal pain (2), dizziness (1), upset stomach (2), rhinitis (2), rash (1), respiratory disorder (1), urticaria (1) and malaise (1). Of the twenty reported adverse events, seven were probably or possibly related to the study drug. In the opinion of the investigators, the other fourteen adverse events were either remotely or unrelated to the study drug. None of the adverse events was considered serious or resulted in dropping any subject from the study participation.

There were no clinically significant changes in the clinical laboratory measurements over the course of the study which could be reasonably associated with the formulations under investigation.

In general, the clinical portion of the project was completed without any significant consequence attributable to the investigational drug. There were no deviations from the volunteer instructions of no prescription medications or nonprescription medications within fourteen or seven days of period I dosing. In general, all blood collections were successfully completed as per protocol design. The clinical laboratory values were considered unremarkable and none of the values outside of the reference range at study exit were considered directly attributable to the product.

The plasma concentrations and pharmacokinetic parameters for acyclovir are summarized below in Table II.

Table II

Mean Plasma Acyclovir Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 Acyclovir Capsule under Fasting and Nonfasting Conditions
(N=18)

Time hr	Treatment A Copley-Test Lot #299Z01 Fasting ng/mL(CV%)	Treatment B Copley-Test Lot #299Z01 Nonfasting ng/mL(CV%)	Treatment C Glaxo Wellcome-Reference Lot #4U1356 Nonfasting ng/mL (CV%)
0	0	0	0
0.25	12.53 (232)	0	0
0.50	136.71 (102)	0	1.58 (424)
0.75	247.63 (66.1)	17.68 (219)	13.23 (322)
1.00	310.63 (50.3)	65.53 (151)	47.32 (189)
1.25	340.28 (46.1)	133.32 (121)	100.49 (116)
1.50	363.94 (46.7)	186.12 (90.6)	176.07 (74.9)
1.75	361.17 (41.9)	239.58 (63.0)	243.34 (51.5)
2.00	371.33 (44.4)	285.96 (45.1)	291.89 (43.8)
2.50	348.11 (46.8)	326.17 (26.6)	321.61 (32.6)
3.00	298.67 (42.3)	323.17 (21.5)	320.06 (28.5)
4.00	233.78 (39.2)	301.22 (22.6)	285.50 (25.9)
6.00	135.33 (40.2)	172.75 (27.4)	155.92 (26.2)
8.00	84.30 (36.8)	96.90 (29.2)	85.97 (26.3)
10.00	52.68 (34.8)	60.43 (27.6)	56.79 (30.1)
12.00	35.10 (35.8)	39.16 (36.8)	38.56 (28.7)
14.00	20.97 (69.7)	22.94 (67.8)	23.99 (49.9)
16.00	10.40 (116)	11.11 (117)	11.57 (104)

	A	B	C	B/C
AUCTLQC (ng.hr/mL)	1985.27(36.5)	1904.24(19.7)	1806.15(24.7)	1.05
AUCinf (ng.hr/mL)	2098.40(34.5)	2027.25(18.6)	1918.78(23.5)	1.06
Cmax (ng/mL)	440.94(38.9)	385.83(23.4)	372.67(25.9)	1.04
Tmax (hr)	1.69	2.67	2.60	
Kel (1/hr)	0.213	0.228	0.219	
T1/2 (hr)	3.34	3.134	3.308	

1. The acyclovir mean plasma levels peaked at 2.5 hours for both the test and reference products, under nonfasting conditions and at 2 hours for the test product under fasting conditions.

2. For Copley's test product, the mean AUCTLQC, AUCinf and Cmax values were 5.4%, 5.7% and 3.5% higher, respectively, than the reference product values under nonfasting conditions. The ratios of

the test arithmetic mean to the reference arithmetic mean are within the acceptable range of 0.8-1.2 for AUCTLQC, AUCinf and Cmax.

3. For the test product, the mean AUCTLQC, AUCinf and Cmax values after dosing with food were about 95.9%, 96.6% and 87.5%, respectively, of the values reported in the fasting state.

VII. Formulation:

Copley's formulation for its Acyclovir 200 mg Capsules are shown in Table III.

VIII. In Vitro Dissolution Testing

Method: USP 23 apparatus 2 (paddle) at 100 rpm
Medium: 900 mL of 0.1 N Hcl
Sampling Time: 5, 10, 15, 20 and 30 minutes.
Test Product: Copley's Acyclovir Capsules, 200 mg, lot #299Z01
Reference Product: Glaxo-Wellcome's Zovirax Capsules, 200 mg, lot #4U1356
Number of Capsules: 12

The dissolution testing results are shown in Table IV.

IX. Deficiency Comment:

The firm is advised to provide dissolution testing data using the method in FDA /PF Volume 22, Number 4, July-August, 1996:

Medium: 900 mL of water
Apparatus I (basket) at 100 rpm

X. Comments:

1. The firm's in vivo bioequivalence studies under fasting and nonfasting conditions are acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUCTLQC, LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions. The ratios of the test mean to the reference mean were within the acceptable range of 0.8-1.2 for AUCTLQC, AUCinf and Cmax under nonfasting conditions.

2. The firm provided dissolution data for the test and reference acyclovir capsules using method other than the FDA/PF method. The firm is advised to submit dissolution testing using the FDA/PF method.

XI. Recommendations:

1. The bioequivalence studies conducted by Copley Pharmaceutical, Inc., under fasting and nonfasting conditions on its Acyclovir, 200 mg Capsules, lot #299Z01, comparing it to Glaxo-Wellcome's Zovirax® 200 mg Capsules have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Copley's Acyclovir Capsules, 200 mg is bioequivalent to the reference product, Zovirax®, 200 mg Capsules, manufactured by Glaxo-Wellcome.

2. The dissolution testing conducting by Copley Pharmaceutical, Inc., on its Acyclovir, 200 mg Capsules, lot #299Z01, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment.

The firm should be informed of the deficiency comment and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 9/6/96

Concur: /S/ Date: 9/13/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/9-5-96 wp 74914SD.696
cc: ANDA #74-914, original, HFD-658 (Makary), Drug File, Division File.

Table IV. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Capsules
Dose Strength: 200 mg
ANDA No.: 74-914
Firm: Copley
Submission Date: June 18, 1996
File Name: 74914SD.696

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: X RPM: 100
No. Units Tested: 12
Medium: 900 mL of 0.1N HCl
Specifications: NLT % in 30 minutes
Reference Drug: Zovirax
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 299Z01 Strength(mg) 200			Reference Product Lot # 4U1356 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
5	42.3		20.1	44.4		25.5
10	87.4		12.8	90.2		9.9
15	100.0		3.7	96.3		4.0
20	101.2		3.0	98.0		3.8
30	101.5		3.0	98.7		3.7

Figure 4.5.1 Linear Plot of Mean Plasma Acyclovir Concentrations *vs* Time

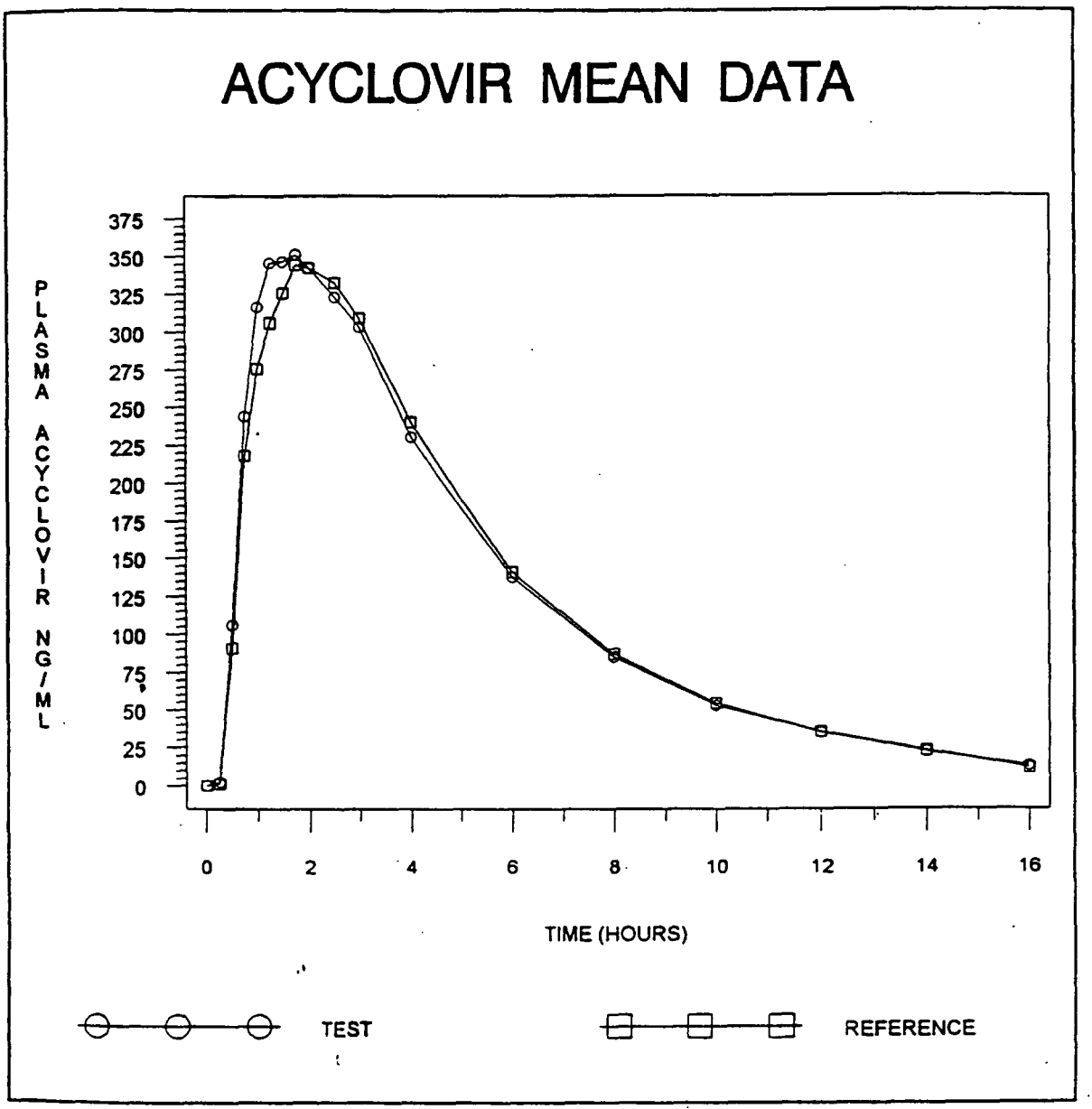

Figure 4.5.1 Linear Plot of Mean Plasma Acyclovir Concentrations *vs* Time