CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-179

BIOEQUIVALENCE

Nabumetone
500 mg & 750 mg Tablets
ANDA #75-179
Reviewer: Z.Z. Wahba
File #75179a.m98

Copley Pharmaceutical, Inc.
Caton, MA
Submission Date:
March 05, 1998
July 16, 1998

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm has previously submitted two in vivo bioequivalence studies (single-dose fasting and single-dose post-prandial) comparing its test product Nabumetone Tablets, 750 mg to the reference listed product SmithKline Beecham's Relafen® Tablets, 750 mg.

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated January 30, 1998, ANDA #75-179) due to a deficiency regarding the dissolution data.

DEFICIENCY COMMENT:

The firm was asked to submit complete dissolution testing data using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of 2% w/v sodium lauryl sulfate (SLS) in water.

THE FIRM'S RESPONSE TO COMMENT:

The dissolution testing for the test and reference products is summarized below:

Apparatus: USP 23 apparatus 2 (Paddles) at 50 rpm
Medium: 900 mL of 2.0% w/v sodium lauryl sulfate (SLS) in water
Test Product: Copley's Nabumetone Tablets, 750 mg, lot #510Z05
Copley's Nabumetone Tablets, 500 mg, lot #510Z03
Ref. Product: SmithKline Beecham's Relafen® Tablets, 750 mg, lot #17995R52
SmithKline Beecham's Relafen® Tablets, 500 mg, lot #9775R51
Number of Units: 12 Tablets

The dissolution testing results are shown in the following table

Table. In Vitro Dissolution Testing

Drug (Generic Name): Nabumetone Tablets
Dose Strength: 750 mg and 500 mg
ANDA No.: 75-179
Firm: Copley Pharmaceutical, Inc.
Submission Date: March 05, 1998
File Name: 75179a.m98

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 2% w/v SLS in water
Reference Drug: SmithKline Beecham's Relafen® Tablets, 750 & 500 mg
Assay Methodology

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Nabumetone Lot #510Z05 Strength(mg) 750			Reference Product Relafen® Lot #17995R52 Strength(mg) 750		
	Mean %	Range	%CV	Mean %	Range	%CV
15	57.6		4.9	42.5		19.3
30	83.7		3.1	77.3		11.3
60	96.2		2.5	96.3		2.3
90	98.1		3.3	98.4		2.3

Sampling Times (Minutes)	Test Product Nabumetone Lot 325Z03 Strength(mg) 500			Reference Product Relafen® Lot #9775R51 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	54.5		7.0	47.2		20.6
30	83.8		4.9	82.9		12.7
60	96.7		2.0	96.9		3.4

90	98.0		1.7	98.4		3.0

COMMENTS ON THE DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI):

1. The firm conducted the dissolution testing on expired reference products, lot #17995R2 (expiration date 11/30/97, dissolution testing date 02/18-23/98) and lot #9775R51 (expiration date 12/31/97, dissolution testing date 02/24-25/98).

2. The dissolution testing data for both the test and reference products pass the specification Q value at 30 minutes.

3. The dissolution profile comparisons meet the F2 values (F2=Similarity Factor) that have been established by the Agency for Post-Approval Changes (Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997).

4. The dissolution data are acceptable.

RECOMMENDATIONS

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Copley Pharmaceutical, Inc. on its Nabumetone Tablet, 750 mg, lot #510Z05, comparing it to the reference listed product, SmithKline Beecham's Relafen® Tablet, 750 mg, have been found acceptable. The two studies demonstrate that under fasting and non-fasting conditions, Copley's Nabumetone Tablet 750 mg is bioequivalent to the reference listed product, SmithKline Beecham's Relafen® Tablets 750 mg.

2. The dissolution testing conducted by Copley Pharmaceutical, Inc. on its drug products, Nabumetone Tablet, 750 mg (lot #510Z05) and 500 mg (lot #325Z03) are acceptable. The waiver of the in vivo bioequivalence study requirements for the 500 mg strength of the test product is granted. The Division of Bioequivalence deems the 500 mg strength of the test product to be bioequivalent to the reference listed product, SmithKline Beecham's Relafen® Tablets 500 mg.

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 2% w/v sodium lauryl sulfate (SLS) in water, at 37°C using Apparatus #2 (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

The firm should be informed of the above recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 7/20/98
FT INITIALLED BDAVIT Barbara M Davit 7/20/98

Concur: Dale P. Conner Date: 7/21/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Nabumetone
500 mg & 750 mg Tablets
ANDA #**75-179**
Reviewer: Z.Z. Wahba
File #75179sdw.897

Copley Pharmaceutical, Inc.
Caton, MA
Submission Date:
August 04, 1997
October 24, 1997

REVIEW OF TWO IN-VIVO BIOEQUIVALENCE STUDIES AND IN VITRO DISSOLUTION TESTING DATA

I. OBJECTIVE:

Review the following:

1. Copley's in vivo bioequivalence study under fasting and non-fasting conditions comparing its drug product Nabumetone Tablets, 750 mg to the reference drug product SmithKline Beecham's Relafen® Tablets, 750 mg.

2. Dissolution data for the 500 mg and 750 mg strengths of test and reference drug products.

3. A Waiver for the 500 mg strength Tablet.

II. INTRODUCTION:

Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties. The drug mode of action is not clear. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect. Nebumetone is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6-MNA), that is a potent inhibitor of prostaglandin synthesis.

Nabumetone is well absorbed from the gastrointestinal tract. Nabumetone itself is not detected in the plasma because, after absorption, it undergoes rapid biotransformation to the principle active metabolite, 6-MNA. Approximately 35% of a 100 mg oral dose of nabumetone is converted to 6-MNA and 50% is converted into unidentified metabolites which subsequently excreted in the urine. Following oral administration of nabumetone, 6-MNA exhibits pharmacokinetics that generally follow a one-compartment model with first order input and first order elimination. 6-MNA is more than 99% bound to plasma proteins. Coadministration of

food increases the rate of absorption and subsequent appearance of 6-MNA in the plasma but does not affect the extent of conversion of nabumetone into 6-MNA.

Nabumetone is marketed as Relafen® Tablets (SmithKline Beecham), 750 mg and 500 mg (NDA #19-583, 12/24/91).

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITION Clinical Study #970535

A. Sponsor:

Copley Pharmaceutical, Inc.
25 John Road
Canton, MA 02021

Study Site:
Clinical, Analytical and Facilities
Phoenix International Life Sciences Inc.
4625 Dobrin Street
Saint-Laurent (Montreal)
Quebec, Canada H4R 2P7

Investigators:
Clinical Investigator: Pierre Geoffrey, M.D.
Study Director: Richard L. Lalonde, Pharm.D.

Blood Samples Collection Dates:
Period I: April 22-27, 1997
Period II: May 13-18, 1997

B. Study design:

Single dose, randomized, two-way crossover study under fasting conditions.

C. Subjects:

Thirty-eight (38) healthy male subjects were enrolled in the study. Subjects #31 and #32 elected to withdraw from the study for personal reasons. Subject #31 withdraw approximately 1 day prior to Period 2 dosing and subject #32 withdraw 15.0 days after Period 1 dosing. Thus, a total of 36 subjects completed the study (subjects #1-30 and #33-38).

The subjects were within 18 to 45 years of age, and their body weights were within ± 15% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:

Only medically and physically healthy subjects with clinically normal ranges of laboratory tests (blood chemistry, hematology, urinalysis) were enrolled in the study.

Subject Exclusion Criteria:

- A history of cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunological, neurological or psychiatric disease.
- A history of peptic ulcer disease.
- A history of drug or alcohol addiction or abuse.
- A history of allergic responses to the class of drug being tested.
- Blood donation or participation in another clinical trial within the past 28 days prior to the study.

Subject Restrictions:

- No subject took any medications, including OTC products for at least 7 days prior to the beginning of the study until completion of the study.
- No alcoholic, xanthine and caffeine containing foods and beverages were allowed, beginning with 24 hours prior to dosing until completion of the study.

D. Food and Fluid Intake:

Subjects fasted overnight for at least 10 hours before dosing and 4 hours after dosing. The doses were administered with 240 mL tap water. Water was not permitted for 1 hour before and 1 hour after the dose, but was allowed at all other times. The subjects received their medication according to a randomized dosing schedule. Standard meals were provided at appropriate times thereafter (at 4 and 9 hours after drug administration).

E. Treatment Plan:

Test product: 1 X 750 mg Copley's Nabumetone Tablet, Lot #510Z05, Batch size Tablets, assay potency: 100.8%, content uniformity: 100.7%, manufacturing date: 4/97.

Reference product: 1 X 750 mg SmithKline Beecham's Relafen® Tablet, Lot #17995R52, assay potency: 100.2%, content uniformity: 100.2, expiration date: 11/30/97.

Washout period: 21 days.
A single 750 mg dose was given in each period of the study.

F. Blood Sampling:

Blood samples (5 mL each) were collected in vacutainers containing EDTA, before dosing (0 hour) and at 0.50, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 16, 24, 36, 48, 72, 96 and 120 hours post-dosing. The plasma samples were separated, collected and stored frozen at -22°C until analysis.

G. Assay Methodology:
(pp #1774-1943, Vol. C1.6, section "Analytical Report")

1. Methods:
The plasma assay of 6-Methoxy-2-Naphthylacetic (6-MNA) was performed by
with fluorescence detection.

The assay validation data are summarized as follows:

2. Sensitivity:
The lower limit of quantitation was 0.1 μg/mL for 6-MNA in human plasma. Samples with assayed values below 0.1 μg/mL were reported as zero.

3. Linearity: 0.10 to 50.08 μg/mL.
Correlation coefficients (r) determined from the calibration curves were ≥ 0.9997 for 6-MNA.

4. Study Validation : (pp #1781-1784, Vol. C1.6)
Results are summarized in the following two tables.

Table #1
Precision and Accuracy for Quality Control Samples for 6-MNA in Plasma

Theoretical Conc. μg/mL	0.30	20.03	40.06
Mean Con.	0.324	21.021	42.013
Precision (%CV)	3.4	2.6	2.6
Accuracy (%)	107.9	104.9	104.9
n	57	57	58

Table #2
Calibration Curve Standards Summary

Theoretical Conc. μg/mL	0.10	0.20	0.50	1.00	7.51	15.02	30.05	45.07	50.08
Mean Con.	0.089	0.189	0.533	1.095	7.814	14.797	29.122	44.462	51.453
Precision (%CV)	8.9	3.9	2.5	4.4	2.9	2.5	2.8	3.6	2.4
Accuracy (%)	89.2	94.4	106.5	109.5	104.1	98.5	96.9	98.7	102.7
n	29	29	29	28	27	29	29	29	29

5. Recovery: (p #1822-1823, Vol. C1.6)

Table #3 Recovery Data

Theoretical Conc. For 6-MNA (μg/mL)	0.30	20.00	40.01
Mean Con.	0.326	21.159	43.762
Precision (%CV)	4.4	2.6	2.1
Accuracy (%)	108.6	105.8	109.37
n	10	10	10

6. Stability: (p #1825-1828, Vol. C1.6)
(The stability data are presented on pages #240-244, Vol. C1.4, section "Analytical Report section").

1. 6-MNA was stable at room temperature (22°C) and during - 4 freeze/thaw cycles.

2. Long term stability data showed that 6-MNA was stable for 216 days at -22°C.

H. In Vivo BE Study and Statistical Analysis:

Thirty-eight (38) healthy male subjects were enrolled in the study. Subjects #31 and #32 elected to withdraw from the study for personal reasons. Thus, a total of 36 subjects completed the study (subjects #1-30 and #33-38).

Adverse Events:

The adverse reactions are reported on page #1261-1263, Vol. C1.4. The following are the summary of adverse events for study subjects under fasting conditions. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

Parameter	Treat A (# of Subjects)	Treat B (# of Subjects)
Headache	2	2
Flatulence	2	--
Runny nose	1	1
Loss of coordination	1	--
Dry lips	1	--
Loss of equilibrium	--	1
Soft stools	--	1

The pharmacokinetic parameters of 6-MNA in plasma were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for the plasma 6-MNA concentrations, as well as the following parameters, AUCt,

AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

Table #4

Mean Plasma Concentrations (μg/mL) of 6-MNA in 36 Subjects Following a Single Oral Dose of 1X750 mg Nabumetone Under Fasting Conditions

(Test Lot #510Z05, Reference Lot #17995R52)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	5.21	3.95	3.26	2.61	1.60
1	10.29	6.24	9.47	6.29	1.09
1.5	12.77	7.28	11.76	7.01	1.09
2	14.44	7.42	13.30	7.82	1.09
3	16.13	8.01	14.96	7.93	1.08
4	16.98	8.09	15.86	8.68	1.07
5	16.96	8.45	14.93	8.07	1.14
6	16.22	7.82	14.93	8.22	1.09
7	15.55	7.49	14.34	7.81	1.08
8	15.37	7.52	14.19	7.90	1.08
9	15.49	7.70	14.01	7.51	1.11
10	14.77	7.43	13.73	7.55	1.08
11	14.38	7.25	13.49	7.21	1.07
12	14.22	7.34	13.29	7.15	1.07
13	14.16	7.36	13.25	7.22	1.07
14	13.90	7.24	13.49	7.43	1.03
16	13.48	7.20	13.28	7.48	1.01
24	12.82	7.48	13.02	7.88	0.98
36	9.39	6.15	9.66	6.71	0.97
48	7.11	5.03	7.37	6.04	0.96
72	3.58	3.34	3.66	3.59	0.98
92	1.80	1.93	1.88	2.22	0.96
120	0.91	1.14	1.00	1.40	0.91

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #5

Mean Pharmacokinetic Parameters (Arithmetic) of 6-MNA in 36 Subjects Following a Single Oral Dose of 1X750 mg Nabumetone Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	828.39	554.08	830.47	614.22	1.00
AUCT	791.56	503.03	789.39	550.96	1.00
CMAX	18.33	8.56	16.70	8.66	1.10
KE	21.86	5.08	21.85	5.39	1.00
*LAUCI	677.19	0.65	659.62	0.68	1.03
*LAUCT	655.56	0.63	637.82	0.66	1.03
*LCMAX	16.24	0.52	14.43	0.57	1.13
THALF	0.03	0.01	0.03	0.01	0.99
TMAX	5.14	5.06	7.58	7.40	0.68

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
* The values represent the geometric means (antilog of the means of the logs).

Table #6
LSMeans And The 90% Confidence Intervals (for 6-MNA) in 36 Subjects Following a Single Oral Dose of 1X750 mg Nabumetone Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	677.19	659.62	1.03	96.13	109.64
LAUCT	655.56	637.82	1.03	96.26	109.75
LCMAX	16.24	14.43	1.13	102.68	123.45

UNIT: AUC=μG HR/ML CMAX=μG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

1. The mean plasma 6-MNA levels reached a maximum level of concentration around 4.0 hours (Table #4 and Figures #1 and 2) for both the test and reference products.

2. The 90% confidence intervals for the LSMeans log-transformed AUCT, AUCI and CMAX were within the acceptable range of 80-125% (Table #6). The T/R mean ratios (RLSM12) for the log-transformed AUCT, AUCI and CMAX were within the acceptable range of 0.8-1.25% (Table #6).

There were no significant period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCT and AUCI. However, there was a significant sequence effect (p less than 0.05) for the log-transformed pharmacokinetic parameters AUCT and AUCI. For the Cmax, there was no significant period effect of the test and reference drug treatments. However, there was a significant sequence and treatment effects (p less than 0.05) for the log-transformed pharmacokinetic parameter Cmax.
The results of the ANOVA test for the presence of sequence effect for LAUCT and LAUCI, and sequence and treatment effects for LCMAX would not affect the determination of bioequivalence (Guidance: Statistical Procedures For Bioequivalence Studies Using A Standard Two-Treatment Crossover Design; dated July 01,1992).

IV. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (clinical study project #970536)

A. Sponsor:

Copley Pharmaceutical, Inc.
25 John Road
Canton, MA 02021

Study Site:
Clinical, Analytical and Facilities
Phoenix International Life Sciences Inc.
4625 Dobrin Street
Saint-Laurent (Montreal)
Quebec, Canada H4R 2P7

Investigators:
Clinical Investigator:
Study Director:

Blood Samples Collection Dates:
Period I: April 17-22, 1997
Period II: May 08-13, 1997
Period III: May 29, 1997 - June 03, 1997

B. Study design:

Randomized, three-way crossover, single dose study, under fasting and non-fasting conditions.

C. Subjects:

Twenty-one (21) healthy male subjects were enrolled for this study. Twenty (20) subjects completed the entire clinical portion of the study (subjects #1-16 and 18-21). Subject #17 elected to withdraw from the study 19.1 days after Period 2 dosing for personal reasons. The subjects were 21 to 44 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Exclusion and Restrictions Criteria:
Same as in study #970535 under fasting conditions

D. **Treatment Plan**:

Test Product:

Treatment A: Under fasting conditions, 1 X 750 mg Copleys's Nabumetone Tablet, Lot #510Z05, Batch size , Tablets, assay potency: 100.8%, content uniformity: 100.7%, manufacturing date: 4/97.

Treatment B: Under non-fasting conditions, 1 X 750 mg Copleys's Nabumetone Tablet, Lot #510Z05, Batch size: Tablets, assay potency: 100.8%, content uniformity: 100.7%, manufacturing date: 4/97.

Treatment C: Under non-fasting conditions, 1 X 750 mg SmithKline Beecham's Relafen® Tablet, Lot #17995R52, assay potency: 100.2%, content uniformity: 100.2, expiration date: 11/30/97.

Washout period: 21 days.
A single 750 mg dose was given in each period of the study.

E. **Drug, Food and Fluid Intake**:

Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Subjects who were fed standard recommended breakfast prior to dosing (treatments B and C) only fasted for 9.5 hours. Treatments B and C differed from treatment A in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. Water was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times. Standard meals were provided at appropriate times thereafter (at 4 and 9 hours after dosing).

F. **Blood Sampling**:

Blood samples (5 mL each) were collected in vacutainers containing EDTA, before dosing (0 hour) and at 0.50, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13,

14, 16, 24, 36, 48, 72, 96 and 120 hours post-dosing. The plasma samples were separated, collected and stored frozen at -22°C°C until analysis.

G. **Assay Methodology**:
Same as in Study #970535 (under fasting conditions).

Within Study Validation : (pp #609-611, Vol. C1.3)
Results are summarized in the following two tables.

Table #7
Precision and Accuracy for Quality Control Samples for 6-MNA in Plasma

Theoretical Conc. μg/mL	0.30	20.03	40.06
Mean Con.	0.325	21.317	42.541
Precision (%CV)	5.7	4.4	4.0
Accuracy (%)	108.3	106.4	106.2
n	38	37	38

Table #8
Calibration Curve Standards Summary

Theoretical Conc. μg/mL	0.10	0.20	0.50	1.00	7.51	15.02	30.05	45.07	50.08
Mean Con.	0.089	0.191	0.530	1.086	7.823	14.887	29.518	44.253	51.161
Precision (%CV)	11.4	4.1	4.2	2.9	4.0	3.2	5.8	3.7	3.8
Accuracy (%)	88.6	95.5	106.0	108.6	104.2	99.1	98.2	98.2	102.2
n	19	18	19	17	19	19	19	19	19

H. **In Vivo BE Study and Statistical Analysis**:
Twenty-one (21) healthy male subjects were enrolled for this study. Twenty (20) subjects completed the entire clinical portion of the study (subjects #1-16 and 18-21). Subject #17 elected to withdraw from the study 19.1 days after

Period 2 dosing for personal reasons. As per protocol, statistical and pharmacokinetic analyses were performed on data from subjects Nos. 1-16 and 18 and 19.

Adverse Events:
The adverse reactions are reported on page #213-218, Vol. C1.1. The following are the summary of adverse events for study subjects under non-fasting conditions. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

Parameter	Treat A (# of Subjects)	Treat B (# of Subjects)	Treat C (# of Subjects)
Headache	1	2	1
Dizzy	1	--	--
Heartburn	1	--	--
Small white spot on right eyelid	1	--	--
Dry lips	--	1	--
Runny nose	--	1	--

The pharmacokinetic parameters of nabumetone were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters of the level of plasma concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the tables below:

Table #9
Mean Plasma Concentrations of 6-MNA (μg/mL) in 18 Subjects Following 1X750 mg Oral Dose of Nabumetone Under Non-Fasting Conditions
(Test Lot #510Z05, Reference Lot #17995R52)

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.5	7.53	4.91	5.26	5.25	3.43	3.65	1.43
1	15.18	6.90	16.25	9.86	15.23	11.51	0.93
1.5	18.75	7.16	22.23	10.64	22.89	13.41	0.84
2	20.15	8.51	25.77	10.61	26.69	11.45	0.78
3	21.14	8.12	28.27	10.51	29.92	11.37	0.75
4	21.06	8.87	29.32	11.04	30.24	9.68	0.72
5	20.77	8.67	27.27	9.40	28.27	9.36	0.76
6	19.19	8.06	24.78	8.35	26.67	8.63	0.77
7	18.72	7.58	23.86	8.07	25.09	8.19	0.78
8	17.63	7.32	23.17	7.34	24.31	8.14	0.76
9	17.92	7.68	22.78	6.67	24.35	8.45	0.79
10	17.40	7.27	21.81	6.84	22.13	7.07	0.80
11	16.85	7.25	20.91	6.70	21.66	6.79	0.81
12	16.40	6.78	19.74	6.01	20.82	7.04	0.83
13	16.13	6.49	19.27	6.03	20.91	7.27	0.84
14	16.34	6.64	19.01	5.93	20.54	7.49	0.86
16	15.86	6.66	17.64	5.68	18.16	6.36	0.90
24	14.71	6.43	14.30	4.99	15.21	5.53	1.03
36	11.13	5.40	9.25	3.15	9.98	4.01	1.20
48	7.92	3.90	6.88	3.35	6.93	3.08	1.15
72	3.96	2.26	3.17	1.45	3.28	1.83	1.25
96	1.96	1.24	1.49	0.80	1.57	0.98	1.32
120	0.96	0.67	0.73	0.44	0.71	0.49	1.31

(CONTINUED)

TIME HR	RMEAN13	RMEAN23
0	.	.
0.5	2.20	1.53
1	1.00	1.07
1.5	0.82	0.97
2	0.75	0.97
3	0.71	0.94
4	0.70	0.97
5	0.73	0.96
6	0.72	0.93
7	0.75	0.95
8	0.73	0.95
9	0.74	0.94
10	0.79	0.99
11	0.78	0.97
12	0.79	0.95
13	0.77	0.92
14	0.80	0.93
16	0.87	0.97
24	0.97	0.94
36	1.12	0.93
48	1.14	0.99

72	1.21	0.97
96	1.25	0.95
120	1.34	1.03

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: PLASMA LEVEL=μG/ML TIME=HRS

Table #10
Mean Pharmacokinetic Parameters
in 18 Subjects Following a Single Oral Dose of
1X750 mg Nabumetone Under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	953.33	417.44	942.11	337.88	985.67	382.03	1.01
AUCT	919.50	396.23	917.39	324.30	954.83	357.50	1.00
CMAX	22.30	8.61	30.97	10.05	32.87	10.58	0.72
KE	22.87	3.34	21.91	3.05	21.67	3.63	1.04
*LAUCI	861.20	0.48	878.00	0.41	908.01	0.44	0.98
*LAUCT	833.31	0.48	856.64	0.40	884.09	0.42	0.97
*LCMAX	20.76	0.39	29.20	0.37	31.07	0.36	0.71
THALF	0.03	0.00	0.03	0.00	0.03	0.01	0.96
TMAX	5.64	6.76	3.58	1.68	3.39	1.78	1.57

(CONTINUED)

PARAMETER	RMEAN13	RMEAN23
AUCI	0.97	0.96
AUCT	0.96	0.96
CMAX	0.68	0.94
KE	1.06	1.01
*LAUCI	0.95	0.97
*LAUCT	0.94	0.97
*LCMAX	0.67	0.94
THALF	0.94	0.98
TMAX	1.66	1.06

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=μG HR/ML CMAX=μG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma 6-MNA levels reached the maximum around 4.0 hours (Table #9 and Figures #3 and #4) for both the test and reference products.

2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #10).

V. **FORMULATION COMPARISON**

(P #2475, Vol. C1.1, Section VII "Components & Composition") and (P #114, Vol. B2.1, Section VII "Components & Composition")

The following table shows the composition of the test product, 750 mg and 500 mg Nabumetone Tablets.

Table #11
Composition of Copley's Nabumetone Tablets

Ingredient	750 mg Tablet		500 mg Tablet	
	mg/Tablet	W/W %	mg/Tablet	W/W %
Nabumetone	750.0	81.52	500.0	81.52
Sodium Starch				
Sodium Lauryl				
Hydroxypropyl				
Water,				
Total				

* Used as a manufacturing aide during granulation. Final product is dried to a moisture limit of

VI. IN VITRO DISSOLUTION TESTING

Method: USP 23 apparatus 2 (Paddles) at 75 rpm
Medium: 1000 mL of DI water/0.75% SLS
Sampling Time: 15, 30, 60, 120 and 180 minutes.
Test Product: Copley's Nabumetone Tablets, 750 mg, lot #510Z05
- Copley's Nabumetone Tablets, 500 mg, lot #510Z03
Ref. Product: SmithKline Beecham's Relafen® Tablets, 750 mg, lot #17995R52
SmithKline Beecham's Relafen® Tablets, 500 mg, lot #9775R51
Number of Units: 12 Tablets
The dissolution testing results are shown in the following table

Table #12 In Vitro Dissolution Testing

Drug (Generic Name): Nabumetone Tablets
Dose Strength: 750 mg and 500 mg
ANDA No.: -75-179
Firm: Copley Pharmaceutical, Inc.
Submission Date: August 04, 1997
File Name: 75179sdw.897

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: 1000 mL DI water/0.75% SLS
Specifications: in 180 minutes
Reference Drug: SmithKline Beecham's Relafen® Tablets, 750 & 500 mg
Assay Methodology

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Nabumetone Lot #510Z05 Strength(mg) 750			Reference Product Relafen® Lot #17995R52 Strength(mg) 750		
	Mean %	Range	%CV	Mean %	Range	%CV
15	52.2		9.6	46.3		16.0
30	69.3		2.7	64.8		4.9
60	76.8		1.6	73.5		4.2
120	82.1		1.5	78.4		1.0

180	83.5	82.0-85.8	1.6	80.3	79.0-82.4	1.5

Sampling Times (Minutes)	Test Product Nabumetone Lot 325Z03 Strength(mg) 500			Reference Product Relafen® Lot #9775R51 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	58.8		4.6	65.8		6.7
30	76.0		1.7	82.2		1.7
60	87.9		1.0	91.1		1.3
120	95.0		0.8	95.3		1.8
180	95.7		3.1	95.9	[illegible]	1.9

1. The dissolution data for the test and reference listed products are not acceptable (see the deficiency section).

VII. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Copley's Nabumetone Tablet 750 mg is bioequivalent to the reference product, SmithKline Beecham's Relafen® Tablets 750 mg. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Copley's Nabumetone Tablet 750 mg is bioequivalent to the reference product, SmithKline Beecham's Relafen® Tablets 750 mg. The ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

3. The formulations of the 750 mg and 500 mg test products are proportional in active and inactive ingredients. The waiver of bioequivalence requirements for the 500 mg strength will not be granted until the firm provides a satisfactory

response to the deficiency cited below.

VIII. DEFICIENCY:

The dissolution testing conducted on nabumetone 750 mg and 500 mg tablets do not meet the Agency's requirements. There is no USP dissolution testing procedure specified for nabumetone tablets. Therefore, the sponsor should conduct dissolution testing following the Agency method:

Apply a validated dissolution method, using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of 2% w/v sodium lauryl sulfate (SLS) in water at 37°C.

The dissolution testing should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

IX. RECOMMENDATION

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Copley Pharmaceutical, Inc. on its Nabumetone Tablets 750 mg, lot #510Z05, comparing it to the reference product SmithKline Beecham's Relafen® Tablets 750 mg, lot #17995R52, have been found acceptable by the Division of Bioequivalence.

2. The in vitro dissolution testing conducted by Copley Pharmaceutical, Inc. on its Nabumetone Tablets 750 mg is incomplete for the reason cited in the deficiency section.

3. The firm should conduct the dissolution testing applying a validated dissolution method, using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of 2% w/v sodium lauryl sulfate (SLS) in water at 37°C.

4. From the bioequivalence point of view, the firm has not met requirements of in vitro dissolution testing.

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: #75-179 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

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

Please submit the dissolution data using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of 2% w/v sodium lauryl sulfate (SLS) in water at 37°C.

The dissolution testing should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

Sincerely yours,

Dale P. Conner

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

Table #13
TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS
(under fasting conditions)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2	0.88	0.85	1.41	1.67	0.87	1.15
2	2	1	1.05	1.05	1.08	0.50	0.97	1.03
3	3	2	1.46	1.46	2.58	2.67	1.01	1.00
4	4	1	0.93	0.93	0.93	0.60	0.96	1.04
5	5	1	0.95	0.95	1.11	0.75	0.94	1.07
6	6	2	1.06	1.06	0.63	8.00	1.05	0.96
7	7	2	1.10	1.10	1.24	0.27	0.98	1.02
8	8	2	1.07	1.07	1.02	1.00	1.02	0.98
9	9	1	1.10	1.10	1.64	0.06	1.01	0.99
10	10	1	0.95	0.96	0.81	1.00	1.08	0.93
11	11	2	1.09	1.08	1.42	1.67	0.93	1.07
12	12	2	1.38	1.39	1.45	1.00	1.13	0.89
13	13	2	1.01	1.00	1.14	3.00	0.96	1.04
14	14	1	2.54	2.53	3.19	0.08	1.07	0.94
15	15	1	0.90	0.91	0.86	1.33	1.09	0.92
16	16	1	1.03	0.98	1.23	0.67	0.80	1.26
17	17	2	1.07	1.10	1.04	1.71	1.21	0.83
18	18	2	1.02	1.02	1.14	1.50	1.01	0.99
19	19	1	1.03	1.03	1.34	2.00	1.04	0.96
20	20	2	0.95	0.95	1.17	0.25	1.09	0.92
21	21	1	0.89	0.90	1.13	1.00	1.08	0.92
22	22	1	1.16	1.16	1.10	0.31	1.04	0.96
23	23	2	0.63	0.64	0.57	0.13	0.95	1.06
24	24	1	1.34	1.35	1.33	0.36	1.12	0.89
25	25	2	0.68	0.68	0.87	0.80	0.91	1.10
26	26	1	0.95	0.94	0.74	0.50	0.91	1.10
27	27	1	0.79	0.78	0.93	0.67	0.94	1.06
28	28	2	0.95	0.95	0.94	1.17	0.97	1.03
29	29	1	0.88	0.88	1.02	2.00	1.09	0.92
30	30	2	1.10	1.11	1.19	0.17	1.09	0.91
31	33	1	0.87	0.85	1.27	1.00	0.88	1.13
32	34	1	1.00	1.01	1.03	2.00	1.05	0.95
33	35	2	0.98	0.97	1.11	1.01	1.01	1.00
34	36	2	1.31	1.30	1.33	2.00	0.99	1.01
35	37	1	0.96	0.96	1.00	0.08	1.01	1.00
36	38	2	1.04	1.05	0.91	1.00	1.00	1.00

Table #14
STATISTICS ON THE TEST/REFERENCE RATIOS
(under fasting conditions)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	36	1.06	0.31	0.63	2.54
RAUCI12	36	1.06	0.31	0.64	2.53
RCMAX12	36	1.19	0.48	0.57	3.19
RTMAX12	36	1.22	1.38	0.06	8.00
RKE12	36	1.01	0.08	0.80	1.21
RTHALF12	36	1.00	0.08	0.83	1.26

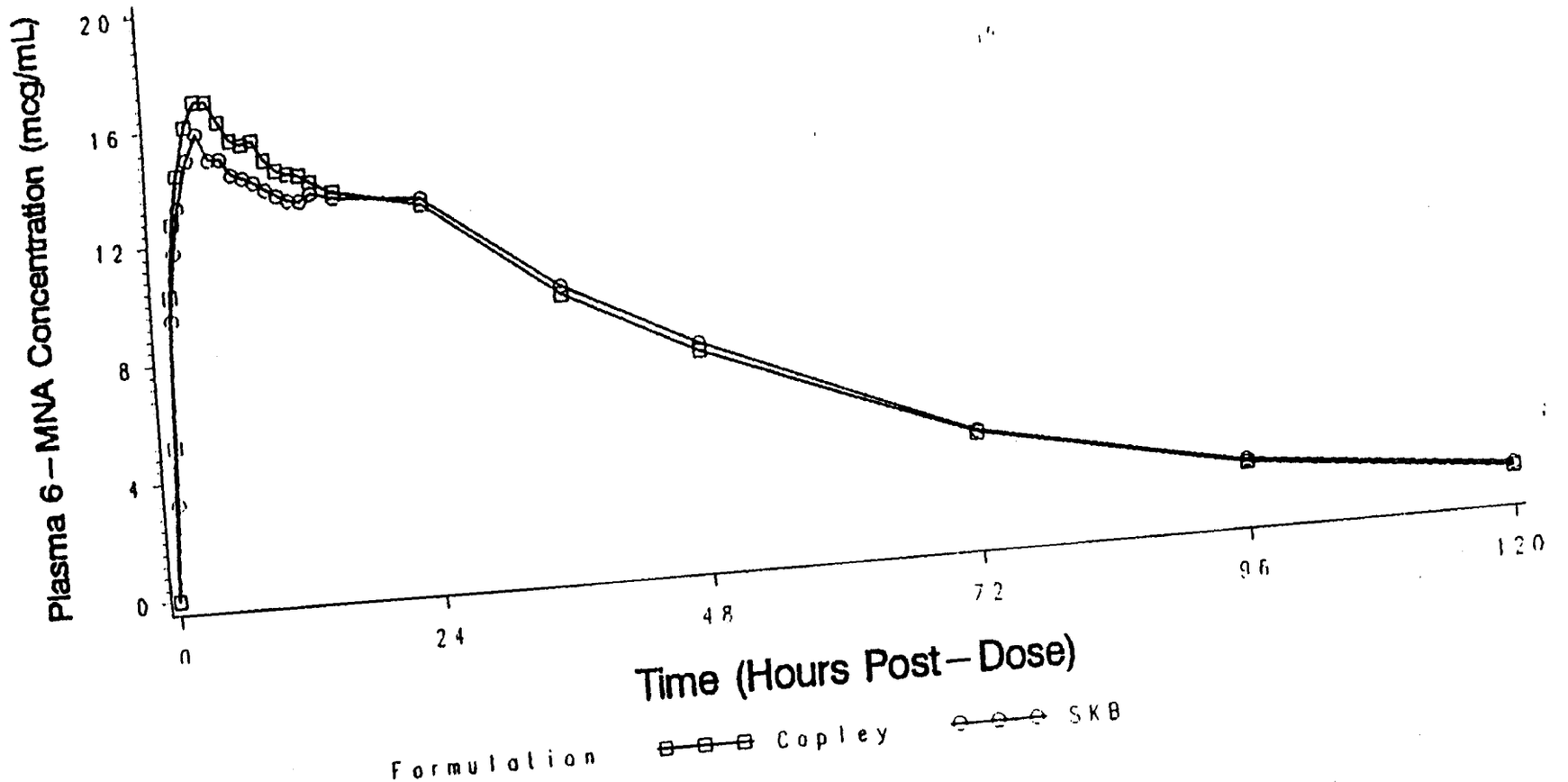
A..DA # 75-179
Nabumetone
Under fasting Conditions

Figure # 1

Project No. 970535

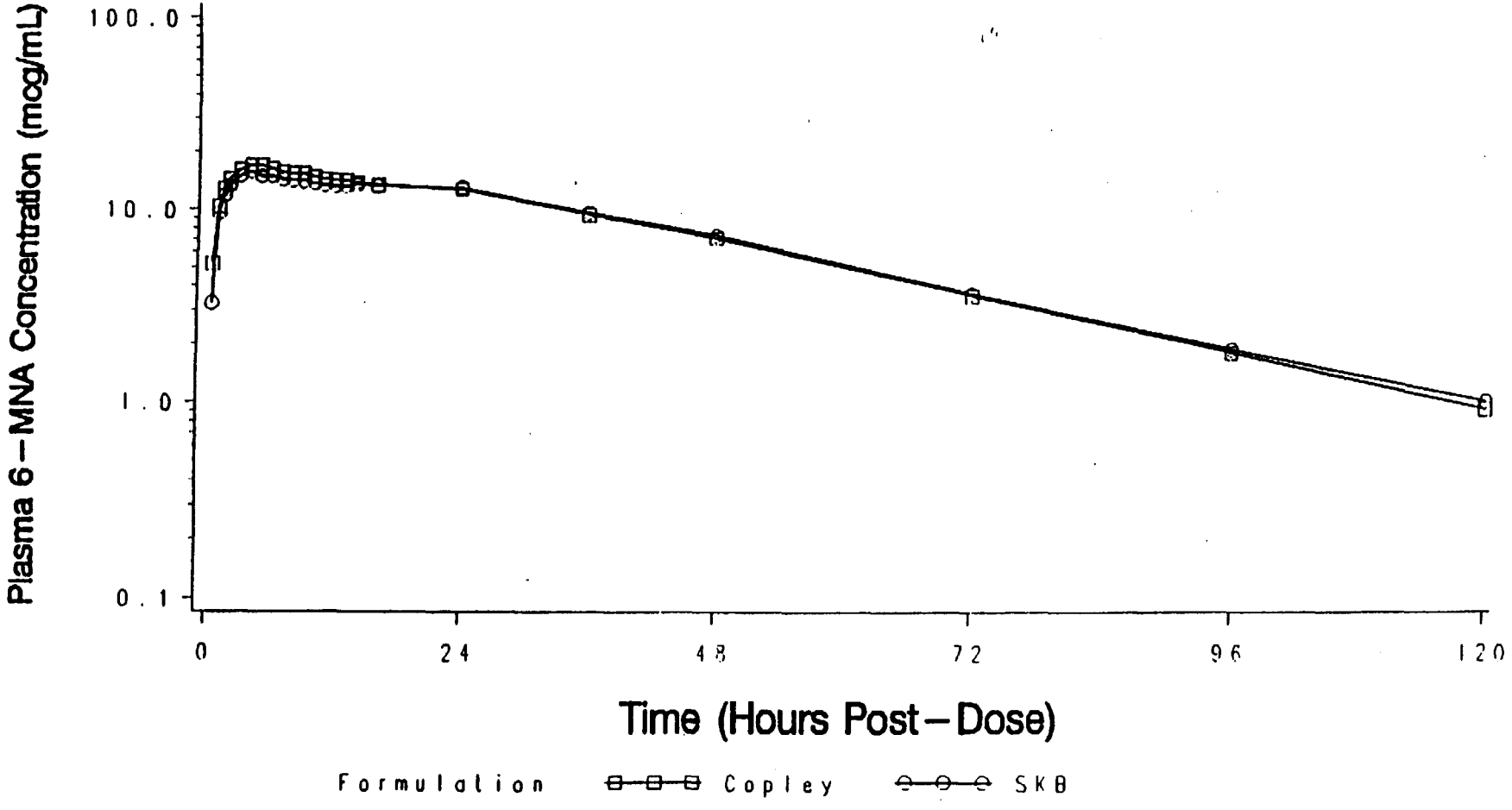
Mean Plasma 6-MNA Concentrations

(Linear Plot)



ANDA # 75-179
Nabumetone
Under fasting Conditions

Figure # 2
Project No. 970535
Mean Plasma 6-MNA Concentrations
(Semi-Log Plot)



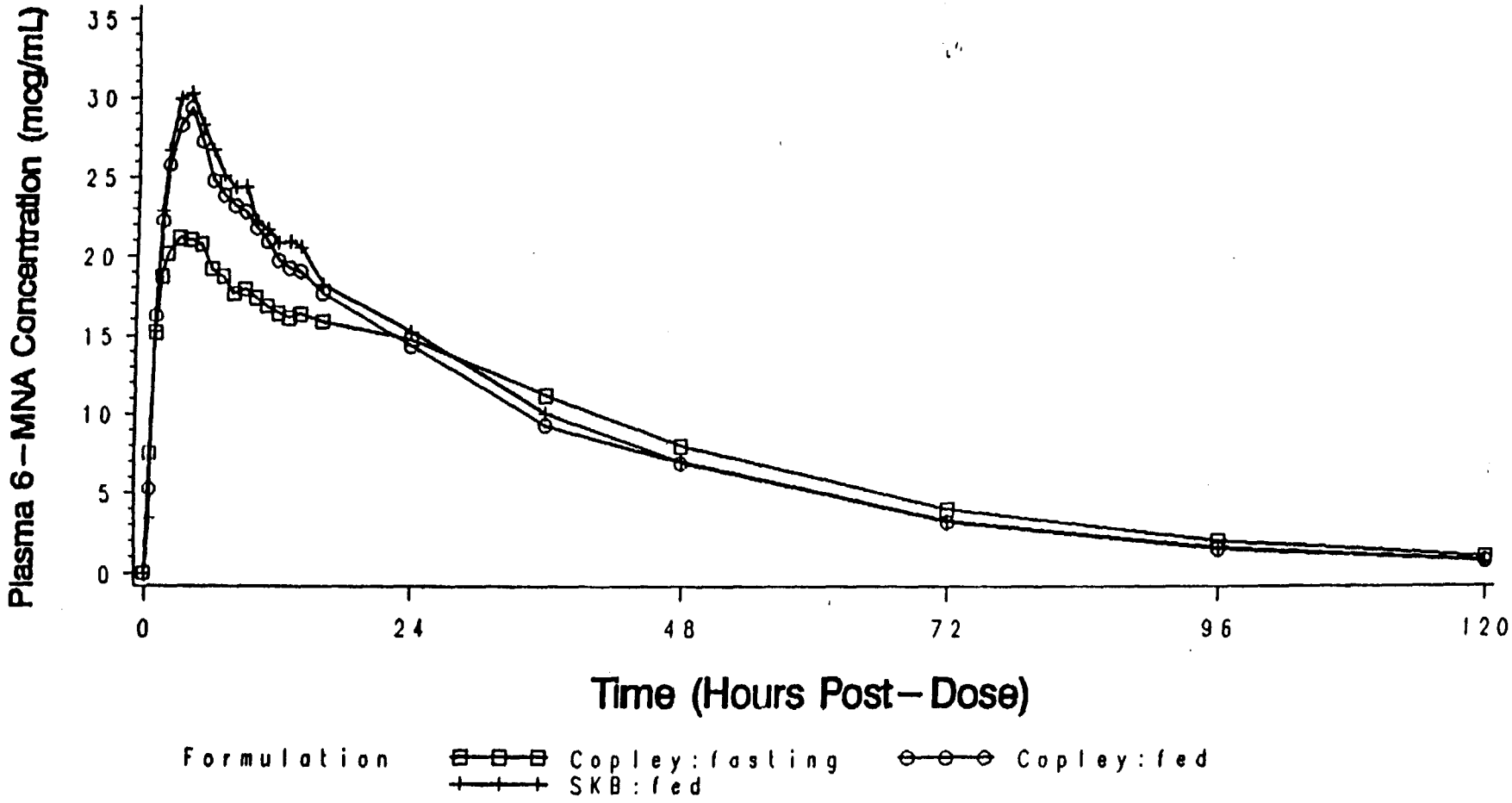
A.N.D.A. # 75-179
Nabumetone
Under Non-Fasting Conditions

Figure # 3

Project No. 970536

Mean Plasma 6-MNA Concentrations

(Linear Plot)



ANDA#75-179
Nabumetone
under non-fasting Conditions

Figure #.4

Project No. 970536

Mean Plasma 6-MNA Concentrations

(Semi-Log Plot)