CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-390

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-390 APPLICANT: Alphapharm

DRUG PRODUCT: Naproxen delayed release tablets
375 mg and 500 mg

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 1000 mL of 0.1N HCl for 120 min (acid stage) and 1000 mL of phosphate buffer pH 6.8 (buffer stage) at 37°C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not more than) of the labeled amount of the drug in the dosage form is dissolved in 120 min (acid stage).

Not less than ' of the labeled amount of the drug in the dosage form is dissolved in 45 minutes (buffer stage).

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,

Barbara M Davit, Ph.D.

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

Naproxen
Delayed-Release Tablets
375 mg and 500 mg
ANDA #75-390
Reviewer: Kuldeep R. Dhariwal
File name: 75390SD.799

Alphapharm Pharmaceuticals
12 Queen Street
P. O. Box 36
Camperdown, NSW 2050
Submission Date:
July 19, 1999
August 12, 1999

Review of an Amendment

Alphapharm has responded to the deficiencies communicated to the firm on bio-studies submitted earlier.

Deficiency 1: Please document the stability of naproxen in frozen plasma samples for 70 days.

Response: The stability of naproxen in frozen plasma samples at -25°C for 14 weeks is documented.

Reviewer's comments: The response is satisfactory.

Deficiency 2: The dissolution testing should be conducted using either method A or method B as described in USP page 1795 and using apparatus II (paddles) at 50 rpm. The sampling times could be 120 min (acid) and 10, 20, 30, 45, and 60 minutes (buffer). To be consistent with USP, please use 0.1N HCl instead of 0.1M HCl. Please provide the mean percentage dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation for each sampling time.

Response: Alphapharm acknowledges the comment concerning the use of method A or method B as described in USP 23 page 1795 using apparatus II (paddles) at 50 rpm for dissolution testing. As requested, 0.1M HCl has been replaced by 0.1N HCl to be consistent with USP.

Reviewer's comments: The firm has opted to use USP method B for dissolution testing. The results are presented in Table 1. The firm submitted dissolution testing data on 375 mg and 500 mg tablets of the reference listed drug in an amendment dated August 12, 1999. The dissolution testing results are acceptable.

NOT TO BE RELEASED UNDER FOI:

The test tablets dissolve faster compared to the reference tablets. Similar trend was seen for Teva's 375 mg tablet and Purepac's 500 mg tablet.

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

7/19/99

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Alphapharm on its naproxen delayed release 375 mg tablet, lot #PM109 comparing it to EC-Naprosyn delayed release tablet, 375 mg, lot #B1439 manufactured by Syntex has been found acceptable by the Division of Bioequivalence. The study demonstrates that Alphapharm's naproxen delayed release 375 mg tablet is bioequivalent to the reference product, EC-Naprosyn delayed release tablet, 375 mg manufactured by Syntex.
2. The *in vivo* bioequivalence study conducted under fasting conditions by Alphapharm on its naproxen delayed release 500 mg tablet, lot #PM108 comparing it to EC-Naprosyn delayed release tablet, 500 mg, lot #B1286 manufactured by Syntex has been found acceptable by the Division of Bioequivalence. The study demonstrates that Alphapharm's naproxen delayed release 500 mg tablet is bioequivalent to the reference product, EC-Naprosyn delayed release tablet, 500 mg manufactured by Syntex.
3. The *in vivo* bioequivalence study conducted under non-fasting conditions by Alphapharm on its naproxen delayed release 500 mg tablet, lot #PM108 comparing it to EC-Naprosyn delayed release tablet, 500 mg, lot #B1286 manufactured by Syntex has been found acceptable by the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Alphapharm's naproxen delayed release 500 mg tablet is similar to that of the reference product, EC-Naprosyn 500 mg tablet manufactured by Syntex.
4. The dissolution testing conducted by the firm on its naproxen delayed release tablets is acceptable. The *in vitro* dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1N HCl for 120 min (acid stage) and 1000 mL of phosphate buffer pH 6.8 (buffer stage) at 37°C using USP apparatus II (paddle) at 50 rpm. The test products should meet the following specifications:

   NMT) of the labeled amount of the drug in the dosage form is dissolved in 120 minutes (acid stage).
   NLT of the labeled amount of the drug in the dosage form is dissolved in 45 minutes (buffer stage).
5. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

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

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR Date 8/30/1999

Concur: Date 8/31/99
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Naproxen Delayed Release Tablet
Dose Strength: 375 mg, 500 mg
ANDA No.: 75-390
Firm: Alphapharm
Submission Date: July 19, 1999
File Name: 75390SD.799

I. Conditions for Dissolution Testing: USP method, page 1795

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl (acid stage), 1000 mL; pH 6.8 phosphate buffer (buffer stage), 1000 mL
Specifications: NMT in 120 min (acid), NLT in 45 min (buffer)
Reference Drug: EC-Naprosyn (Syntex)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PM109 Strength(mg) 375			Reference Product Lot # B1439 Strength(mg) 375		
	Mean %	Range	%CV	Mean %	Range	%CV
Acid: 120	0		0	0		0
Buffer: 10	0		147.7	1		118.2
20	57		25.6	10		70.4
30	92		6.3	70		16.4
45	97		3.0	100		2.3
60	97		2.1	102		1.4

Sampling Times (Minutes)	Test Product Lot # PM108 Strength(mg) 500			Reference Product Lot # B1286 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
Acid: 120	0		0	0		0
Buffer: 10	1		215.3	0		0
20	51		38.1	3		115.7
30	89		7.4	60		42.4
45	96		3.9	99		3.0
60	98		2.9	101		101

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-390 APPLICANT: Alphapharm

DRUG PRODUCT: Naproxen delayed release tablets
375 mg and 500 mg

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 1000 mL of 0.1N HCl for 120 min (acid stage) and 1000 mL of phosphate buffer pH 6.8 (buffer stage) at 37°C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not more than of the labeled amount of the drug in the dosage form is dissolved in 120 min (acid stage).

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

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,

Barbara M Sanit, Ph. D.

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

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-390 APPLICANT: Alphapharm Pharmaceuticals

DRUG PRODUCT: Naproxen Delayed Release Tablets, 375 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:

1. Please document the stability of naproxen in frozen plasma samples for 70 days.

2. The dissolution testing should be conducted using either method A or method B as described in USP 23 page 1795 and using apparatus II (paddles) at 50 rpm. The sampling times could be 120 min (acid) and 10, 20, 30, 45, and 60 minutes (buffer). To be consistent with USP, please use 0.1N HCl instead of 0.1M HCl. Please provide the mean percentage dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation for each sampling time.

3. Please provide the theoretical and actual yield of biostudy lots of both strengths.

4. Please provide T_{lag} and the adjusted T_{max} data for all biostudies.

5. Please note for future studies that sample analysis should not begin before completing the clinical 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

NOV 30 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-390 APPLICANT: Alphapharm Pharmaceuticals

DRUG PRODUCT: Naproxen Delayed Release Tablets, 375 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:

1. Please document the stability of naproxen in frozen plasma samples for 70 days.

2. The dissolution testing should be conducted using either method A or method B as described in USP 23 page 1795 and using apparatus II (paddles) at 50 rpm. The sampling times could be 120 min (acid) and 10, 20, 30, 45, and 60 minutes (buffer). To be consistent with USP, please use 0.1N HCl instead of 0.1M HCl. Please provide the mean percentage dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation for each sampling time.

3. Please provide the theoretical and actual yield of biostudy lots of both strengths.

4. Please provide T_{lag} and the adjusted T_{max} data for all biostudies.

5. Please note for future studies that sample analysis should not begin before completing the clinical 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

Naproxen
Delayed-release tablets
375 mg and 500 mg
ANDA #75-390
Reviewer: Kuldeep R. Dhariwal
File name: 75390SD.798

Alphapharm Pharmaceuticals
12 Queen Street
P. O. Box 36
Camperdown, NSW 2050
Submission Date:
July 31, 1998

REVIEW OF THREE BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA

The firm has submitted the results of three bioequivalence studies comparing its test product naproxen 375 mg and 500 mg delayed-release (DR) tablets (enteric-coated) with the reference product EC-Naprosyn® 375 mg and 500 mg delayed-release tablets (Syntex) under fasting (for 375 mg and 500 mg tablets) and non-fasting conditions (for 500 mg tablet). The firm has also submitted comparative dissolution profiles on 375 and 500 mg strengths of its product and reference listed drug EC-Naprosyn® 375 and 500 mg delayed-release (enteric-coated) tablets.

Introduction:

EC-Naprosyn® is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis. EC-Naprosyn® is not recommended for initial treatment of acute pain.

Naproxen is available in several forms, including delayed-release, enteric-coated tablets. Naproxen is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring in 4-6 hours after an oral dose of EC-Naprosyn® tablets. The elimination half-life is 12-17 hours. The extent of naproxen absorption (AUC) and peak plasma levels (C_{max}) are not significantly affected when EC-Naprosyn® is taken with food, but the time to peak (T_{max}) is delayed up to 12 hours.

Bioequivalence Study On Naproxen 375 mg Tablets Under Fasting Conditions:

A. Study Information:

Protocol#:	1843
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	Biovail Corporation, Canada
Principal Investigator:	Paul Y. Tam, M.D.
Analytical Facility:	Biovail Corporation, Canada
Analytical Director:	David McDonald, Ph.D.
Study Dates:	Subjects 0-21: Period I June 1, 1997 Period II June 15, 1997 Subjects 22-26: Period I June 15, 1997 Period II June 29, 1997
Analysis Dates:	June 19 to July 14, 1997
Study Design:	Randomized, two-way crossover design with a wash-out period of 14 days
Randomization Scheme:	AB: 4,5,6,7,10,11,13,16,17,19,22,24,25 BA: 1,2,3,8,9,12,14,15,18,20,21,23,26

Treatments:

A: Naproxen DR (Enteric coated) Tablets, 1x375 mg; Alphapharm Pharmaceutical; Lot #PM109A; Lot Size: not given; Manufacture Date: 21/2/97; Assay: 102.1%

B: EC-Naprosyn® Tablets (Enteric coated), 1x375 mg; Syntex; Lot #B1439; Expiry Date: 10/99; Assay: 100.9%

Formulation of Test Product: Table 1

Subjects:	26 healthy male subjects (24 plus 2 alternates) were enrolled in the study according to inclusion/exclusion criteria specified in the protocol. However, only 21 qualified subjects were available on May 31, 1997. Therefore 5 additional subjects were enrolled on June 14, 1997. All subjects completed the study. Samples from only first 24 subjects were analyzed as per the protocol.
Housing:	From the evening before dosing until after 24 hour blood draw. Subjects returned for subsequent blood draws.

Dosing: After 10 hour fast, with 240 mL of water. Water was not allowed within one hour of dosing. No food for 4.5 hours post-dose.

Sample Collection: Blood samples (1x10 mL) were collected into heparinized Vacutainers at predose (0 h) and at following times post-dose: 0.50, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 14, 18, 24, 36, 48, and 72 hours.

B. Study Results:

1. Clinical:

Drop-outs: None.

Adverse Events: One adverse event was reported. Subject #20 experienced nausea about 2 hours after dosing in period I (reference product).

Protocol Deviations: There were three sampling time deviations. Pharmacokinetic parameters were calculated using the scheduled times. This should not change the results too much.

2. Analytical: **NOT TO BE RELEASED UNDER FOI**

Method:

Internal Standard:

Linearity: Weighted linear regression analysis (1/concentration). Correlation coefficients were greater than 0.998 for naproxen.
Std. curve range: 0.50-128.01 µg/mL

QC samples: 0.75, 1.50, 12.0, and 96.01 µg/mL

Accuracy: Standards: 96.09% to 101.9%
QC samples: 95.75% to 102.58%

Precision: Standards: 2.25% to 3.27%
QC samples: 3.49% to 5.84%

Reassays: Five samples were repeated for pharmacokinetic reasons.

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

Linearity: Std. curve range: 0.50-128 µg/mL
Correlation coefficients were greater than 0.9987.

Accuracy:

Inter-day	Standards	96.6%-101.37%
	QC samples	96.0%-100.5%
Intra-day	QC samples	89.3%-102.0%

Precision:	Inter-day	Standards	2.46%-6.64%
		QC samples	1.22%-8.38%
	Intra-day	QC samples	1.83%-5.82%

Specificity: Thirteen blank plasma samples from different individuals did not show any interference at the retention times of naproxen and internal standard.

Recovery:	0.75 µg/mL	91.5%
	1.50 µg/mL	93.6%
	12.0 µg/mL	94.3%
	96.0 µg/mL	92.1%
	IS	77.0%

Stability:
a) room temperature: Plasma samples were left at room temperature for 5.6 hours and then extracted and analyzed. Naproxen was stable.
b) long term stability: Firm states that studies are in progress. No long term stability data were submitted.
c) freeze-thaw: Stable over 4 cycles.
d) Naproxen was stable in extracted samples stored in the autosampler at room temperature for 24 hours.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	97.63%-102.64%
	$LAUC_{0-inf}$	97.77%-103.24%
	LC_{max}	88.57%-100.50%
Test/Reference Ratios:	AUC_{0-t}	0.90-1.19 (mean 1.00)
	AUC_{0-inf}	0.85-1.22 (mean 1.00)
	C_{max}	0.66-1.49 (mean 0.96)
AUC_{0-t}/AUC_{0-inf} Ratios:	Test	0.84-0.98 (mean 0.94)
	Reference	0.88-0.98 (mean 0.94)

Comments:

1. The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.

2. No subjects with 0 h drug level, no subjects with first scheduled post-dose time point as T_{max}, and no subjects with first measurable drug concentration as C_{max}.

3. **NOT TO BE RELEASED UNDER FOI:** The protocol required that 26 subjects be enrolled in the study. However, only 21 qualified subjects were available at the start of the study. Therefore, 5 additional subjects were later enrolled. Following were the dosing periods of all the subjects:

Subject #	Period I	Period II
1-21	June 1	June 15
22-26	June 15	June 29

The reviewer discussed the statistical analysis with Dr. Chuanpu Hu of QMR staff.

4. **NOT TO BE RELEASED UNDER FOI:**

5. **NOT TO BE RELEASED UNDER FOI:** The reviewer, however, also analyzed the data using model GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT TRT*GRP. The TRT*GRP effect was statistically significant (p=0.0154) for LC_{max}. The significance of this was discussed with Dr. Hu.

6. Sample analysis started before completing the clinical study.

7. The firm has not provided theoretical and actual yield of bio-lot.

8. The firm has not provided T_{lag} and the adjusted T_{max}.

9. The firm has not documented stability of naproxen in frozen plasma samples for 45 days.

10. The fasting study is incomplete.

Bioequivalence Study On Naproxen 500 mg Tablets Under Fasting Conditions:

A. Study Information:

Protocol#:	1805-1
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	Biovail Corporation, Canada
Principal Investigator:	Paul Y. Tam, M.D.
Analytical Facility:	Biovail Corporation, Canada
Study Dates:	Period I April 13, 1997 Period II April 27, 1997
Analysis Dates:	May 2 to June 3, 1997
Study Design:	Randomized, two-way crossover design with a wash-out period of 14 days
Randomization Scheme:	AB: 1,2,3,4,8,13,14,17,18,19,21,22,25 BA: 5,6,7,9,10,11,12,15,16,20,23,24,26

Treatments:

A: Naproxen DR (Enteric coated) Tablets, 1x500 mg; Alphapharm Pharmaceutical; Lot #PM108A; Lot Size: not given; Manufacture Date: 31/1/97; Assay: 101%

B: EC-Naprosyn® Tablets (Enteric coated), 1x500 mg; Syntex; Lot #B1286; Expiry Date: 08/99; Assay: 102.6%

Formulation of Test Product: Table 1

Subjects: 26 healthy male subjects (24 plus 2 alternates) were enrolled in the study according to inclusion/exclusion criteria specified in the protocol. All subjects completed the study. Samples from only first 24 subjects were analyzed as per the protocol.

Housing: From the evening before dosing until after 24 hour blood draw. Subjects returned for subsequent blood draws.

Dosing: After 10 hour fast, with 240 mL of water. Water was not allowed within one hour of dosing. No food for 4.5 hours post-dose.

Sample Collection: Same as for fasting study on 375 mg tablet.

B. Study Results:

1. Clinical:

Drop-outs: None.

Adverse Events: Two adverse events (dizziness and headache) were reported.

Protocol Deviations: 1.There were two sampling deviations. Pharmacokinetic parameters were calculated using the scheduled times. This should not change the results too much.
2. One subject consumed caffeine containing cola during the study.

2. Analytical: **NOT TO BE RELEASED UNDER FOI**

Method:

Internal Standard:

Linearity: Weighted linear regression analysis (1/concentration). Correlation coefficients were greater than 0.999 for naproxen.
Std. curve range: 0.50-128.01 µg/mL

QC samples: 0.75, 1.50, 12.0, and 96.01 µg/mL

Accuracy: Standards: 96.29% to 102.3%
QC samples: 94.67% to 104.66%

Precision: Standards: 2.01% to 5.19%
QC samples: 3.41% to 12.07%

Reassays: All samples of subject #10 were repeated for pharmacokinetic reasons.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations: Table 3 and Figure 2

Pharmacokinetic Parameters: Table 3

90% Confidence Intervals:

$LAUC_{0-t}$	99.65%-106.12%
$LAUC_{0-inf}$	99.89%-106.55%
LC_{max}	89.47%-107.37%

Test/Reference Ratios:	AUC_{0-t}	0.89-1.33	(mean 1.03)
	AUC_{0-inf}	0.91-1.36	(mean 1.04)
	C_{max}	0.55-1.63	(mean 1.01)
AUC_{0-t}/AUC_{0-inf} Ratios:	Test	0.90-0.98	(mean 0.94)
	Reference	0.88-0.98	(mean 0.94)

Comments:

1. The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.

2. No subjects with 0 h drug level and no subjects with first scheduled post-dose time point as T_{max}. Subject numbers 1,16, and 21 had first measurable drug concentration (at 5h) as C_{max} on test product. These subjects were not excluded from analysis because this is a delayed release product.

3. The firm has not provided theoretical and actual yield of bio-lot.

4. The firm has not provided T_{lag} and the adjusted T_{max}.

5. The firm has not documented stability of naproxen in frozen plasma samples for 50 days.

6. The fasting study is incomplete.

Bioavailability of Naproxen Under Non-Fasting Conditions:

A. Study Information:

Protocol#:	1806	
IRB Approval:	Yes	
Consent Form Signed:	Yes	
Clinical Site:	Biovail Corporation, Canada	
Principal Investigator:	Paul Y. Tam, M.D.	
Analytical Facility:	Biovail Corporation, Canada	
Study Dates:	Period I	April 3, 1997
	Period II	April 17, 1997
	Period III	May 1, 1997
Analysis Dates:	May 7 to June 13, 1997	
Study Design:	Randomized, three-way crossover design with a wash-out period of 14 days	
Randomization Scheme:	ABC: 3,4,17	
	BCA: 1,15,18	

CAB: 2,8,9
ACB: 5,6,16
BAC: 10,11,13
CBA: 7,12,14

Treatments:

A: Naproxen DR (Enteric coated) Tablets, 1x500 mg; Alphapharm Pharmaceutical; Lot #PM108A; administered after a standard breakfast

B: EC-Naprosyn® Tablets (Enteric coated), 1x500 mg; Syntex; Lot #B1286; administered after a standard breakfast

C: Naproxen DR (Enteric coated) Tablets, 1x500 mg; Alphapharm Pharmaceutical; Lot #PM108A; administered after an overnight fast

Formulation of Test Product: Table 1

Subjects: 21 healthy male subjects (18 plus 3 alternates) were enrolled in the study according to inclusion/exclusion criteria specified in the protocol. All subjects completed the study. Samples from only first 18 subjects were analyzed as per the protocol.

Housing: From the evening before dosing until after 24 hour blood draw. Subjects returned for subsequent blood draws.

Dosing: Treatment A and B: After an overnight fast and 30 minutes prior to dosing, subjects were given OGD approved standardized breakfast. The drug was administered 5 minutes after subjects finished the breakfast.
Treatment C: After an overnight fast, with 240 mL of water.
Water was not allowed within one hour of dosing. No food for 4.5 hours post-dose.

Sample Collection: Same as for fasting study on 500 mg tablet.

B. Study Results:

1. Clinical:

Drop-outs: None.

Adverse Events: Six adverse events (fatigue and pain in cheeks) were reported.

Protocol Deviations: There were few sampling deviations. Pharmacokinetic parameters were calculated using the scheduled times. This should not change the results too much.

2. Analytical: **NOT TO BE RELEASED UNDER FOI**

Method:

Internal Standard:

Linearity: Weighted linear regression analysis (1/concentration). Correlation coefficients were greater than 0.999 for naproxen.
Std. curve range: 0.50-128.01 µg/mL

QC samples: 0.75, 1.50, 12.0, and 96.01 µg/mL

Accuracy: Standards: 96.2% to 102.0%
QC samples: 97.86% to 104.91%

Precision: Standards: 2.53% to 4.06%
QC samples: 3.09% to 4.62%

Reassays: One sample was repeated due to low internal standard response.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations: Table 4, Figure 3

Pharmacokinetic Parameters: Table 5

AUC_{0-t}/AUC_{0-inf} Ratios:

Test fasting	0.94	(0.90-0.97)
Test Non-fasting	0.92	(0.88-0.96)
Ref. Non-fasting	0.93	(0.87-0.97)

Comments:

1. The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.

2. No subjects with 0 h drug level and no subjects with first scheduled post-dose time point as T_{max}. Subject numbers 1 and 18 under test non-fasting conditions; 1, 2 and 9 under reference non-fasting conditions; and number 7 under test fasting conditions had first measurable drug concentration as C_{max}. These subjects were not excluded from analysis because this is a delayed release product.

3. Seven subjects (#4,5,6,10,11,12,13) on test non-fasting treatment and 4 subjects (#5,7,11,12) on reference non-fasting

treatment had 4 or less data points. The reviewer omitted these subjects and reanalyzed the data from remaining **10 subjects**. Ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} remained within acceptable limits. The decision on this study can be taken from the data from only 10 evaluable subjects because

a) this is a delayed release product and it is common phenomenon to see some subjects with only 3 or 4 data points.
b) this is a food study where 'n' is usually smaller than fasting study.
c) the study is acceptable if the subjects with 4 or less data points are not excluded from the analysis.

4. The elimination constant and therefore AUC_{0-inf} could not be calculated for subject #5,10, and 13 for test non-fasting, and for #5 and 7 for reference non-fasting. The reviewer agrees with this observation.

5. The firm has not documented stability of naproxen in frozen plasma samples for 70 days.

6. The non-fasting study is incomplete.

In Vitro Dissolution Testing:

Apparatus:	I, 100 rpm
Media:	Initially 0.1M HCl, 1000 mL and then pH 6.8 phosphate buffer, 1000 mL
Results:	Table 6

Comments:

1. The dissolution testing conducted by the firm is not acceptable. The dissolution testing should be done using either method A or method B as described in USP 23 page 1795 using **apparatus II (paddles) at 50 rpm**. The sampling times should be 120 min (acid) and 10, 20, 30, 45, and 60 minutes (buffer).

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Alphapharm on its naproxen delayed release 375 mg tablet, lot #PM109A comparing it to EC-Naprosyn® delayed release tablet, 375 mg, lot #B1439 manufactured by Syntex has been found incomplete by the Division of Bioequivalence.

2. The bioequivalence study conducted under fasting conditions by Alphapharm on its naproxen delayed release 500 mg tablet, lot #PM108A comparing it to EC-Naprosyn® delayed release tablet, 500 mg, lot #B1286 manufactured by Syntex has been found incomplete by the Division of Bioequivalence.

3. The bioequivalence study conducted under non-fasting conditions by Alphapharm on its naproxen delayed release 500 mg tablet, lot #PM108A comparing it to EC-Naprosyn® delayed release tablet, 500 mg, lot #B1286 manufactured by Syntex has been found incomplete by the Division of Bioequivalence.

4. The dissolution testing conducted by the firm on its 375 mg and 500 mg tablets is not acceptable.

5. The study is incomplete.

Dhariwal

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
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Date 11/6/98

Concur: Dale P. Conner Date 11/12/98
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Director, Division of Bioequivalence

Table 1

Composition of Naproxen Delayed Release Tablets

Ingredient	mg/tablet	
	375 mg	500 mg
Naproxen	375	500
Croscarmellose Sodium		
Povidone		
Magnesium Stearate		
Sodium Hydroxide		
Methacrylic Acid Copolymer		
Purified Talc		
Polyethylene Glycol		
Titanium Dioxide		
Simethicone		
Total core weight		

Table 2

Mean Plasma Naproxen Levels For Test (1) and Reference (2) Products
In Fasting Study On 375 mg Tablet, n=24

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	0.00	0.00	0.00	0.00	.
1	0.19	0.78	0.00	0.00	.
1.5	2.13	5.50	3.33	7.82	0.64
2	15.76	20.23	10.52	19.05	1.50
2.5	30.56	24.96	20.04	22.82	1.52
3	37.46	24.85	30.30	25.00	1.24
3.5	40.12	22.06	42.76	21.21	0.94
4	40.19	20.03	47.87	19.61	0.84
5	42.20	11.93	45.89	15.59	0.92
6	40.98	6.35	41.24	8.84	0.99
7	37.87	6.34	37.40	6.99	1.01
8	34.46	6.34	34.28	6.52	1.01
9	31.89	5.90	32.23	6.13	0.99
10	31.31	5.90	30.39	5.74	1.03
12	25.92	5.36	26.06	4.78	0.99
14	23.07	4.48	22.79	4.28	1.01
18	18.15	4.35	17.64	3.51	1.03
24	14.86	4.07	15.00	3.43	0.99
36	9.54	3.37	9.45	2.97	1.01
48	5.44	2.43	5.58	2.22	0.97
72	2.35	1.28	2.29	1.13	1.03

UNIT: PLASMA LEVEL=MICROGRAM/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	977.27	232.36	971.11	204.61	1.01
AUCT	913.61	190.35	910.93	170.86	1.00
CMAX	55.17	10.59	58.54	11.92	0.94
KE	0.04	0.01	0.04	0.01	0.99
LAUCI	951.12	0.24	950.11	0.22	1.00
LAUCT	894.39	0.21	895.24	0.19	1.00
LCMAX	54.27	0.18	57.17	0.23	0.95
THALF	17.32	3.05	17.06	2.69	1.02
TMAX	4.21	1.62	3.98	1.45	1.06

UNIT: AUC=MICROGRAM HR/ML CMAX=MICROGRAM/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1014.45	1003.87	1.01		
AUCT	936.29	931.33	1.00		
CMAX	54.55	58.14	0.94		
LAUCI	6.89	6.89	1.00	97.77	103.24
LAUCT	6.81	6.81	1.00	97.63	102.65
LCMAX	3.97	4.02	0.98	88.57	100.50

Table 3

MEAN PLASMA NAPROXEN LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS
IN FASTING STUDY ON 500 MG TABLET, N=24

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	0.22	1.07	0.49	2.41	0.44
1	0.58	1.90	4.01	13.43	0.15
1.5	8.60	16.39	8.56	22.20	1.00
2	23.35	30.01	21.71	31.94	1.08
2.5	30.57	31.99	32.19	33.52	0.95
3	37.42	30.14	38.70	29.06	0.97
3.5	39.33	28.98	47.44	23.83	0.83
4	38.47	28.06	51.12	21.38	0.75
5	49.50	25.02	55.95	16.05	0.88
6	50.28	17.27	49.86	14.83	1.01
7	45.95	12.99	44.22	12.66	1.04
8	43.31	8.95	40.13	10.93	1.08
9	39.93	9.01	37.01	10.25	1.08
10	38.60	8.16	34.08	8.97	1.13
12	34.38	9.00	31.66	7.17	1.09
14	29.97	8.58	29.04	6.92	1.03
18	23.75	6.43	22.67	6.19	1.05
24	19.18	4.98	18.49	5.01	1.04
36	11.57	3.53	11.01	3.42	1.05
48	6.96	2.31	6.57	2.27	1.06
72	2.82	1.20	2.66	1.19	1.06

UNIT: PLASMA LEVEL=MICROGRAM/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1206.26	238.38	1173.05	243.91	1.03
AUCT	1133.80	205.80	1105.75	213.55	1.03
CMAX	68.47	14.25	69.58	12.99	0.98
KE	0.04	0.00	0.04	0.00	0.98
LAUCI	1185.19	0.19	1148.85	0.21	1.03
LAUCT	1116.81	0.18	1086.02	0.19	1.03
LCMAX	66.98	0.22	68.34	0.20	0.98
THALF	17.18	1.93	16.85	1.81	1.02
TMAX	4.46	2.67	4.31	2.10	1.03

UNIT: AUC=MICROGRAM HR/ML CMAX=MICROGRAM/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1206.26	1173.05	1.03	99.92	105.74
AUCT	1133.80	1105.75	1.03	99.63	105.45
CMAX	68.47	69.58	0.98	90.10	106.71
LAUCI	1185.19	1148.85	1.03	99.89	106.55
LAUCT	1116.81	1086.02	1.03	99.65	106.12
LCMAX	66.98	68.34	0.98	89.47	107.37

Table 4

MEAN PLASMA NAPROXEN LEVELS (microgram/mL) FOR TEST AND REFERENCE PRODUCTS
IN NON-FASTING STUDY, N=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.5	0.08	0.33	0.00	0.00	0.03	0.13	.
1	6.95	15.64	0.00	0.00	1.44	6.12	.
1.5	21.88	31.51	0.18	0.78	2.73	11.59	119.36
2	32.80	30.24	2.50	10.60	2.72	11.54	13.13
2.5	42.33	26.80	2.83	12.00	3.39	14.37	14.97
3	48.05	28.63	2.91	12.33	3.12	13.25	16.53
3.5	46.59	25.07	3.47	14.72	2.88	12.20	13.43
4	47.09	19.28	3.46	14.52	2.70	11.47	13.61
5	53.60	17.30	15.02	28.86	6.61	15.51	3.57
6	50.27	16.20	29.16	34.87	30.30	32.93	1.72
7	45.30	15.01	25.43	29.92	33.29	31.69	1.78
8	40.52	12.55	23.73	25.54	30.33	26.74	1.71
9	38.37	11.63	24.77	26.46	33.86	26.18	1.55
10	36.85	11.10	22.77	24.56	31.72	24.35	1.62
12	35.51	12.00	22.40	21.49	28.57	18.84	1.59
14	30.78	6.99	20.29	18.52	28.65	18.98	1.52
18	23.81	4.74	18.33	16.92	22.17	14.26	1.30
24	19.87	3.61	29.62	24.11	25.98	18.77	0.67
36	12.47	2.69	21.50	10.45	19.04	10.31	0.58
48	7.49	1.76	12.59	5.59	10.97	5.18	0.60
72	3.04	1.02	5.01	2.32	4.23	2.05	0.61

(CONTINUED)

MEAN PLASMA NAPROXEN LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.5	2.63	0.00
1	4.82	0.00
1.5	8.01	0.07
2	12.06	0.92
2.5	12.50	0.84
3	15.39	0.93
3.5	16.20	1.21
4	17.41	1.28
5	8.11	2.27
6	1.66	0.96
7	1.36	0.76
8	1.34	0.78
9	1.13	0.73
10	1.16	0.72
12	1.24	0.78
14	1.07	0.71
18	1.07	0.83
24	0.76	1.14
36	0.66	1.13
48	0.68	1.15
72	0.72	1.18

1= Test Fasting
2= Test Non-Fasting
3= Reference Non-Fasting

Table 5

NAPROXEN ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY ON 500 MG TABLET, N=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	1280.43	188.94	1333.52*	238.58	1278.76**	203.26	0.96
AUCT	1200.30	158.08	1169.34	212.60	1156.71	176.44	1.03
CMAX	71.26	13.26	63.45	15.88	64.69	12.87	1.12
KE	0.04	0.01	0.04	0.00	0.04	0.01	1.00
LAUCI	1266.74	0.15	1313.47	0.18	1263.15	0.16	0.96
LAUCT	1190.10	0.14	1151.14	0.18	1143.72	0.16	1.03
LCMAX	70.08	0.19	61.32	0.28	63.31	0.22	1.14
THALF	17.57	2.50	17.40	1.77	17.17	1.92	1.01
TMAX	4.08	2.57	16.17	11.77	12.58	10.38	0.25

(CONTINUED) * n=15, ** n=16

UNIT: AUC=MICROGRAM HR/ML CMAX=MICROGRAM/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.00	1.04
AUCT	1.04	1.01
CMAX	1.10	0.98
KE	0.98	0.98
LAUCI	1.00	1.04
LAUCT	1.04	1.01
LCMAX	1.11	0.97
THALF	1.02	1.01
TMAX	0.32	1.28

UNIT: AUC=MICROGRAM HR/ML CMAX=MICROGRAM/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	1280.43	1348.74	1282.49	0.95	1.00	1.05
AUCT	1200.30	1169.34	1156.71	1.03	1.04	1.01
CMAX	71.26	63.45	64.69	1.12	1.10	0.98
LAUCI	1266.74	1331.67	1268.10	0.95	1.00	1.05
LAUCT	1190.10	1151.14	1143.72	1.03	1.04	1.01
LCMAX	70.08	61.32	63.31	1.14	1.11	0.97

1= Test Fasting
2= Test Non-Fasting
3= Ref. Non-Fasting

Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Naproxen Delayed Release Tablets
Dose Strength: 375 mg and 500 mg
ANDA No.: 75-390
Firm: Alphapharm
Submission Date: July 31, 1998
File Name: 75390SD.798

I. Conditions for Dissolution Testing: Firm's method

USP XXIII Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium: 0.1M HCl (acid stage), 1000 mL; pH 6.8 phosphate buffer
Volume: 1000 mL; Specifications: NMT 120 min (acid), NLT in 60 minutes (buffer)
Reference Drug: EC-Naprosyn®
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PM 108 Strength(mg) 500			Reference Product Lot # B1286 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
120	0			0		
10	0			0		
20	84			18		
30	101			88		
40	101			100		
60	101			101		

Sampling Times (Minutes)	Test Product Lot # PM 109 Strength(mg) 375			Reference Product Lot # B1439 Strength(mg) 375		
	Mean %	Range	%CV	Mean %	Range	%CV
120	0			0		
10	0			1		
20	82			39		
30	99			92		
40	99			101		
60	99			101		

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-390 APPLICANT: Alphapharm Pharmaceuticals

DRUG PRODUCT: Naproxen Delayed Release Tablets, 375 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:

1. Please document the stability of naproxen in frozen plasma samples for 70 days.

2. The dissolution testing should be conducted using either method A or method B as described in USP 23 page 1795 and using apparatus II (paddles) at 50 rpm. The sampling times could be 120 min (acid) and 10, 20, 30, 45, and 60 minutes (buffer). To be consistent with USP, please use 0.1N HCl instead of 0.1M HCl. Please provide the mean percentage dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation for each sampling time.

3. Please provide the theoretical and actual yield of biostudy lots of both strengths.

4. Please provide T_{lag} and the adjusted T_{max} data for all biostudies.

5. Please note for future studies that sample analysis should not begin before completing the clinical study.

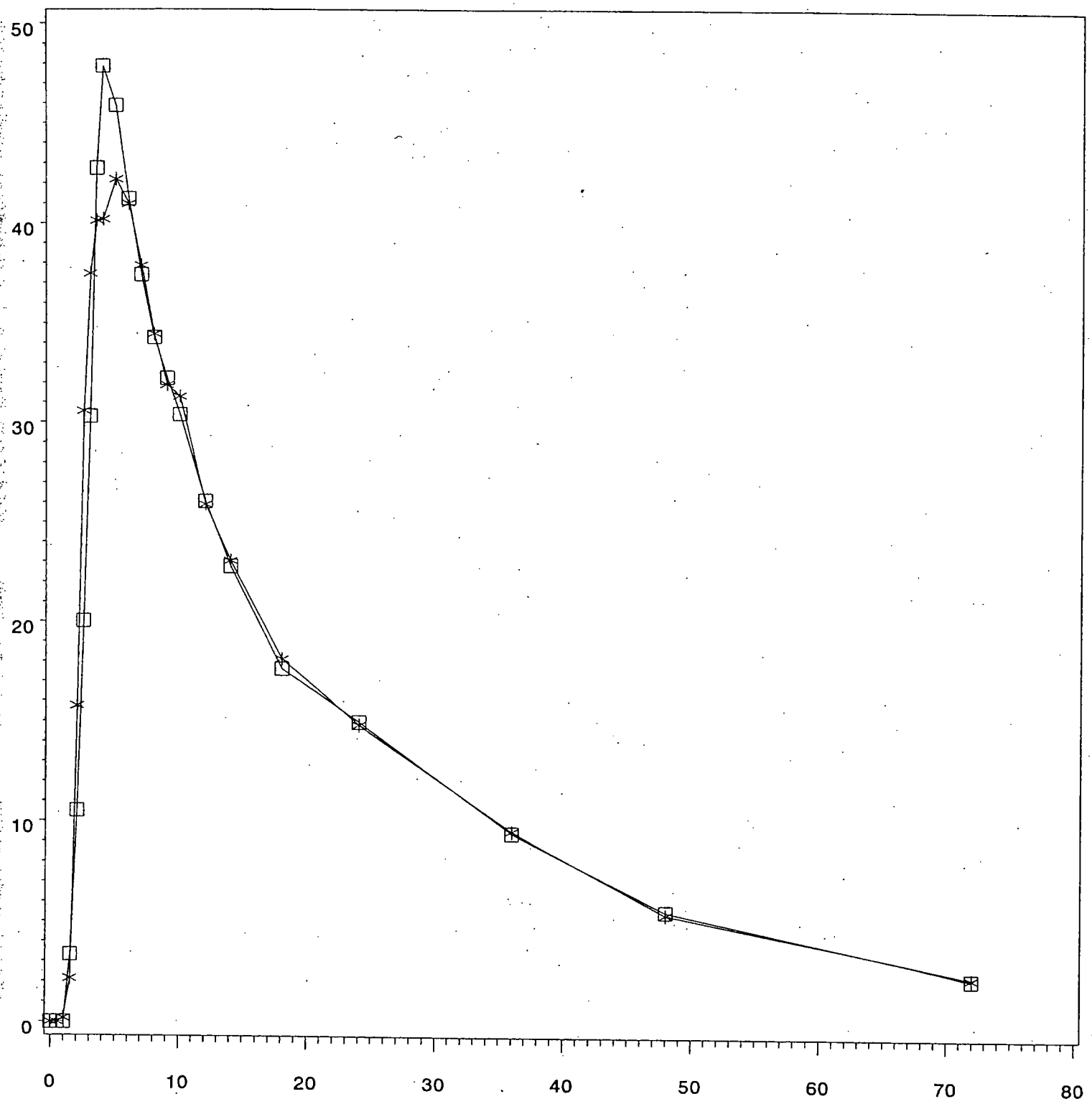
Sincerely yours,

Dale P. Conner

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

FIG 1. PLASMA NAPROXEN LEVELS

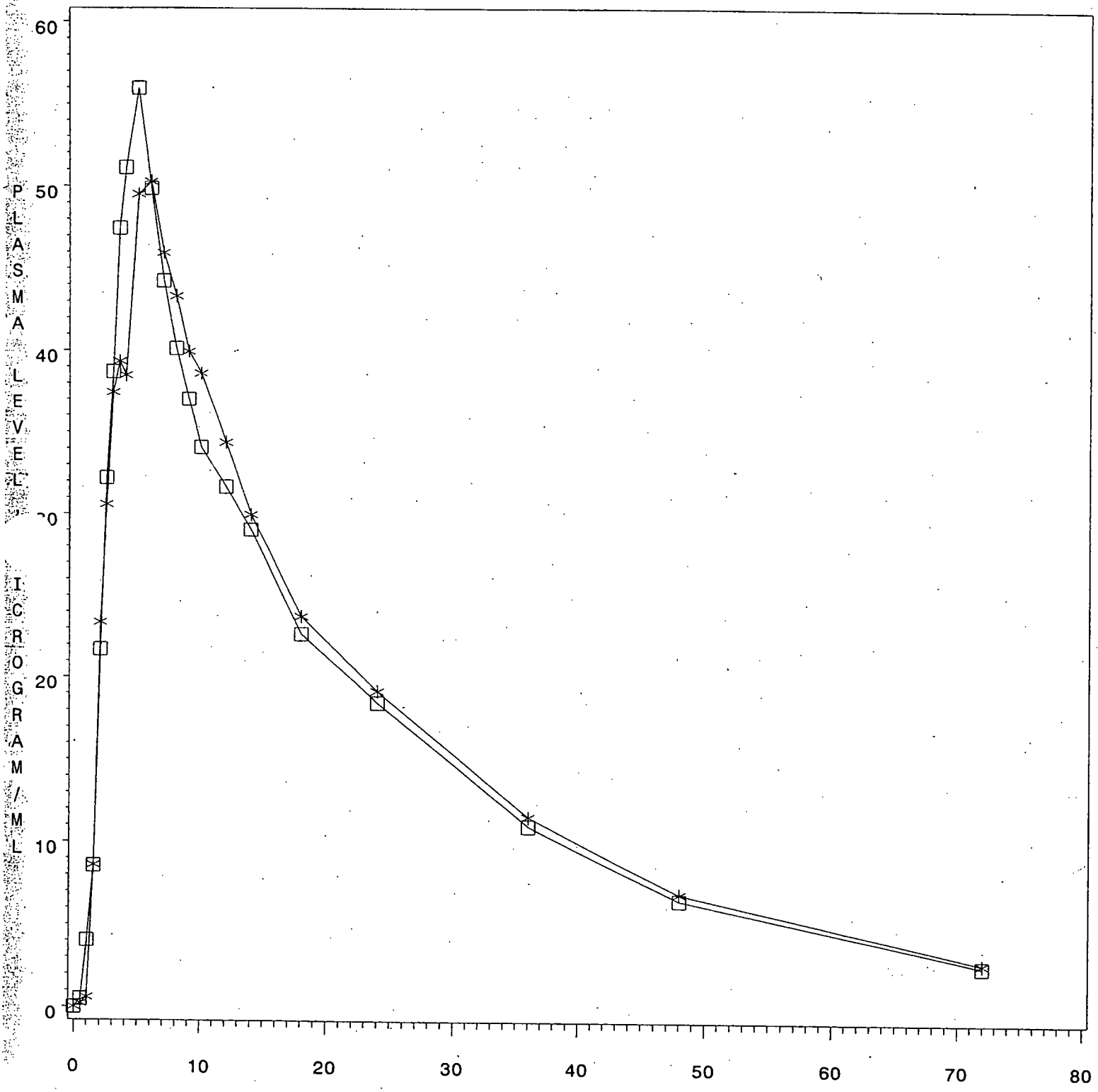
NAPROXEN DELAYED RELEASE TABLETS, 375 MG, ANDA #75-390
UNDER FASTING CONDITIONS
DOSE=1 X 375 MG



1=TEST(ALPHAPHARM) 2=REF(SYNTEX)

FIG 2. PLASMA NAPROXEN LEVELS

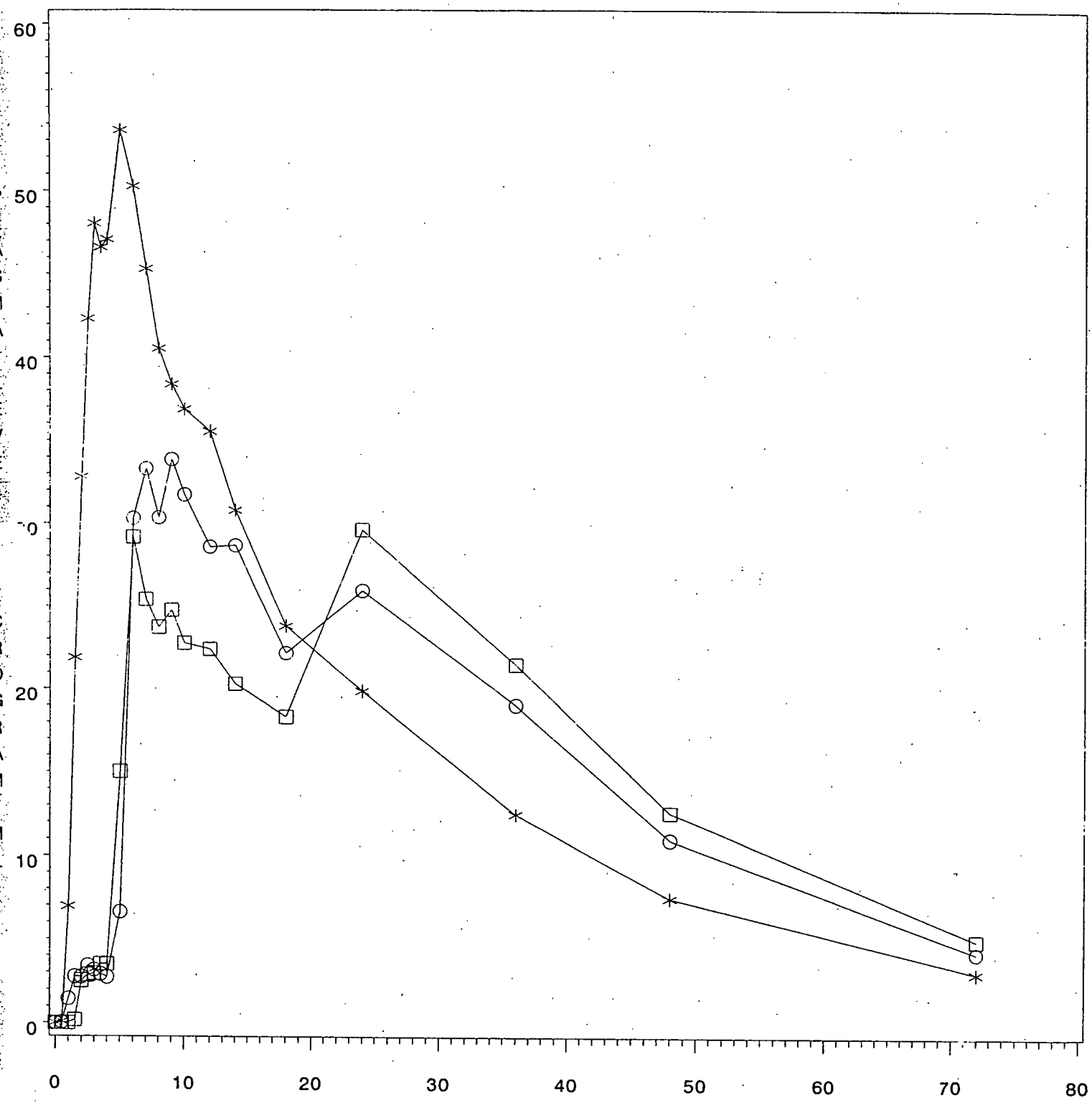
NAPROXEN DR TABLETS, 500 MG, ANDA #75-390
UNDER FASTING CONDITIONS
DOSE=1 X 500 MG



1=TEST(ALPHAPHARM) 2=REF(SYNTEX)

FIG 3. PLASMA NAPROXEN LEVELS

NAPROXEN DR TABLETS, 500 MG, ANDA #75-390
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 500 MG



1=TEST(FAST) 2=TEST(FED) 3=REF(FED)