CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-602

Bioequivalence Review(s)

Aminocaproic Acid Tablets
ANDA #75-602: 500 mg
Reviewer: Hoainhon Nguyen
W #75602add.d00

Mikart, Inc.
Atlanta, GA
Submission Date:
~~March 21, 2000~~
~~April 28, 2000~~
September 5, 2000

Review Addendum: Review of Form FDA 483 and Inspection Report

The single-dose, fasting bioequivalence study for the test product was originally submitted on May 14, 1999. A study amendment was submitted on March 21, 2000 in response to the review deficiency comments on the May 14, 1999 submission. The amendment was found acceptable and the study was therefore found acceptable. The DBE requested an Inspection for this ANDA on 7/1/99, since the firm's product is the First Generic Product of Aminocaproic acid (See Comment #4 in the review of the May 14, 1999 submission).

The reviewer received the September 5, 2000 inspection report and Form FDA 483 (dated March 6-10, 2000 for the clinical facility and June 19-23, 2000 for the analytical facility) for review on September 14, 2000. The clinical facility was AAI International Clinical Research, Chapel Hill, NC, and the analytical facility was

The DSI investigators found the one item that might have affected the study outcomes: *"Accuracy of the assay method for aminocaproic acid in plasma was not demonstrated in that freeze/thaw (F/T) stability experiments do not reflect the handling of the subject samples. F/T stability of aminocaproic acid has not been established in that F/T experiments used "accelerated" freezing (dry ice/acetone) and thawing (warm water) while subject samples were frozen in a –20C freezer and were thawed at room temperature. In response to the Form 483, proposed to conduct additional F/T stability experiments by the end of September 2000. As of this writing* [September 5, 2000] *, the additional data have not been received by DSI."*

The DBE reviewer has allowed additional time for the above-mentioned additional F/T data to be submitted to the DSI, and has been in contact with the DSI through the project manager, Krista Scardina. However, as of this date of the review addendum, December 6, 2000, the data have never arrived, according to Dr. Jaqueline O'Shaughnessy, the DSI investigator. The purpose of this review

addendum is to request the additional F/T data through the sponsor, Mikart Inc. At this time, the bio study is found **incomplete** pending the results of the additional F/T data.

Recommendation: At this time, the single-dose, fasting bio study, Study Protocol No. VER-701, conducted by Mikart Inc. on the test product, Aminocaproic Acid Tablets USP, 500 mg, lot # A980053A, comparing it with the reference product, Immunex (Lederle)'s Amicar® Tablets, 500 mg, lot # 449-362, is found **incomplete** pending the results of the additional F/T data. The recommendation below will be forwarded to the sponsor, Mikart Inc.

Upon reviewing the results of the recent FDA inspection of the clinical facility, AAI Clinic, Chapel Hill, NC (March 6-10, 2000) and the analytical facility, (June 19-23, 2000), for the single-dose, fasting bioequivalence study of your test product, Study Protocol No. VER-701, the Division of Bioequivalence has found the following deficiencies:

Accuracy of the assay method for aminocaproic acid in plasma was not demonstrated in that freeze/thaw (F/T) stability experiments do not reflect the handling of the subject samples. F/T stability of aminocaproic acid has not been established in that F/T experiments used "accelerated" freezing (dry ice/acetone) and thawing (warm water) while subject samples were frozen in a –20C freezer and were thawed at room temperature.

In response to the Form 483 proposed to conduct additional F/T stability experiments by the end of September 2000. To date, the Division of Scientific Investigations and the Division of Bioequivalence have not received the additional F/T experiment data. The data from boratory should be forwarded to both divisions of the Agency.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 12/18/2007

Concur: Barbara M Davit Date: 12/22/07

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

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BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-602 APPLICANT: Mikart Inc.

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 500 mg

Upon reviewing the results of the recent FDA inspection of the clinical facility, AAI Clinic, Chapel Hill, NC (March 6-10, 2000) and the analytical facility, (June 19-23, 2000), for the single-dose, fasting bioequivalence study of your test product, Study Protocol No. VER-701, the Division of Bioequivalence has found the following deficiencies:

Accuracy of the assay method for aminocaproic acid in plasma was not demonstrated in that freeze/thaw (F/T) stability experiments do not reflect the handling of the subject samples. F/T stability of aminocaproic acid has not been established in that F/T experiments used "accelerated" freezing (dry ice/acetone) and thawing (warm water) while subject samples were frozen in a -20°C freezer and were thawed at room temperature.

In response to the Form 483, proposed to conduct additional F/T stability experiments by the end of September 2000. To date, the Division of Scientific Investigations and the Division of Bioequivalence have not received the additional F/T experiment data. The data from laboratory should be forwarded to both divisions of the Agency for review.

Sincerely yours,

for Barbara Myers Davit

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

BIOEQUIVALENCY COMMENTS

ANDA: 75-602 APPLICANT: Mikart Inc.

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 500 mg

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

The Division of Bioequivalence acknowledges that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

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,

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

3.1

Aminocaproic Acid Tablets USP
ANDA #75-602: 500 mg
Reviewer: Hoainhon Nguyen
W #75602a.201

Mikart, Inc.
Atlanta, GA
Submission Date:
February 8, 2001

Review of a Study Admendment and a DSI Report Supplement

I. Submission History:

The single-dose, fasting bioequivalence study for the test product was originally submitted on May 14, 1999. A study amendment was submitted on March 21, 2000 in response to the review deficiency comments on the May 14, 1999 submission. The amendment was found acceptable and the study was therefore found acceptable. The DBE requested an Inspection for this ANDA on 7/1/99, since the firm's product is the First Generic Product of Aminocaproic acid (See Comment #4 in the review of the May 14, 1999 submission).

The reviewer received the September 5, 2000 inspection report and Form FDA 483 (dated March 6-10, 2000 for the clinical facility and June 19-23, 2000 for the analytical facility) for review on September 14, 2000. The clinical facility was AAI International Clinical Research, Chapel Hill, NC, and the analytical facility was

The DSI investigators found the one item that might have affected the study outcomes: *"**Accuracy of the assay method for aminocaproic acid in plasma was not demonstrated in that freeze/thaw (F/T) stability experiments do not reflect the handling of the subject samples.** F/T stability of aminocaproic acid has not been established in that F/T experiments used "accelerated" freezing (dry ice/acetone) and thawing (warm water) while subject samples were frozen in a –20C freezer and were thawed at room temperature. In response to the Form 483, proposed to conduct additional F/T stability experiments by the end of September 2000. As of this writing* [September 5, 2000] *, the additional data have not been received by DSI."*

On January 19, 2001, the DBE informed the firm that the additional F/T stability data had not been submitted to the Agency as previously committed by the contract laboratory, , and that the bio study has now been found **incomplete** pending the results of the additional F/T data.

In the current amendmen submitted the additional F/T stability data. The data were also submitted to the DSI and reviewed by the Division's investigator, Jaqueline A. O'Shaughnessy. The DSI issued a supplement memorandum to the DBE providing its review conclusion (February 14, 2001).

Comments on s additional F/T stability data and the DSI report supplement are as follows.

II. Comments:

1. The firm used more appropriate freeze/thaw conditions for the new stability study compared with the original F/T stability study. The tested QC samples were stored at –20C for at least 12 hours and then thawed unassisted at room temperature. The cycle was repeated 5 times. Some of the samples were extracted and analyzed at the end of first, third and fifth cycle while the remaining samples were transferred back to the original freezer and kept frozen for 12 to 24 hours. The F/T QC samples were compared to Time Zero QC samples. The QC samples that were kept at –20C for the length of the study (5 days) and did not go through the F/T cycles were also compared with Time Zero QC.

The QC sample concentrations were 3.00 ng/mL and 80.0 mg/mL. The difference in concentrations found after 1, 3 and 5 F/T cycles was less than 5% when compared with Time Zero values. The difference in concentrations between 5-day stored QCs and Time Zero QCs was less than 6.1%.

The new F/T stability study is acceptable.

2. The DSI investigator has also concluded similarly *"The additional experiments have demonstrated F/T stability of aminocaproic acid under the conditions of sample handling"* and *"Analytics response has provided adequate F/T stability data for aminocaproic acid. The data should be accepted for your review."*

3. The single-dose, fasting biostudy for the test product is now considered **acceptable.** The Division of Bioequivalence has no further questions at this time.

III. Recommendation:

1. The single-dose, fasting bioequivalence study conducted by Mikart Inc. on the test product, Aminocaproic Acid Tablets USP, 500 mg, lot # A980053A, comparing it with the reference product, Immunex (Lederle)'s Amicar® Tablets, 500 mg, lot # 449-362, has now been found **acceptable.** The study demonstrates that the test product, Mikart's Aminocaproic Acid Tablets, 500 mg, is bioequivalent to the reference product, Immunex's Amicar® Tablets, 500 mg, under fasting conditions.

As found in the review of the submission dated March 17, 1999:

2. The *in vitro* dissolution testing conducted by Mikart on its Aminocaproic Acid Tablets, 500 mg, has been found **acceptable.**

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIV apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 3/2/2001

Concur: Date: 3/8/2001
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS

ANDA: 75-602 APPLICANT: Mikart Inc.

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 500 mg

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

The Division of Bioequivalence acknowledges that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

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,

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

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BIOEQUIVALENCY DEFICIENCIES

JAN 19 2001

ANDA: 75-602 APPLICANT: Mikart Inc.

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 500 mg

Upon reviewing the results of the recent FDA inspection of the clinical facility, AAI Clinic, Chapel Hill, NC (March 6-10, 2000) and the analytical facility, (June 19-23, 2000), for the single-dose, fasting bioequivalence study of your test product, Study Protocol No. VER-701, the Division of Bioequivalence has found the following deficiencies:

Accuracy of the assay method for aminocaproic acid in plasma was not demonstrated in that freeze/thaw (F/T) stability experiments do not reflect the handling of the subject samples. F/T stability of aminocaproic acid has not been established in that F/T experiments used "accelerated" freezing (dry ice/acetone) and thawing (warm water) while subject samples were frozen in a -20°C freezer and were thawed at room temperature.

In response to the Form 483, roposed to conduct additional F/T stability experiments by the end of September 2000. To date, the Division of Scientific Investigations and the Division of Bioequivalence have not received the additional F/T experiment data. The data from laboratory should be forwarded to both divisions of the Agency for review.

Sincerely yours,

Barbara Myers Davit

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

OCT 15 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-602 APPLICANT: Mikart Inc.

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 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. You stated that the long-term stability study of Aminocaproic acid in the frozen plasma samples (stored at -20° C), and the stability studies of stock solutions of Aminocaproic acid and internal standard in are in progress. Please submit results of these studies.

2. All of the pre-dose samples for both periods 1 and 2 were re-assayed (pages 353-354 in volume 2 of 5). The reason(s) should be explained.

3. You stated that Chromatographic peaks showed sometimes jagged peak shape, due to the acquisition conditions.

Please clarify this statement and explain why only <u>some</u> of the chromatographic peaks showed jagged peak shape.

4. Formulas used for calculations of CV%, Accuracy, and Stability data are incorrect (examples: pages 358, 359, and 745 in volume 2 of 5). The corrected data should be submitted.

5. Calculation of %recovery for the internal standard is incorrect (according to the formula provided in page 756, volume 2 of 5). The corrected data should be submitted.

6. Assayed potency data should be submitted for the lot of the reference product used in the bioequivalence study.

Sincerely yours,

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

Aminocaproic Acid
Tablets USP, 500 mg
ANDA #75-602
Reviewer: F. Nouravarsani
W: 75602SD.599

Mikart Inc.
Atlanta, Georgia
Submission letter Dates:
March 17, 1999 (refused to file)
May 14, 1999

REVIEW OF A BIOEQUIVALENCE STUDY AND DISSOLUTION TESTING

INTRODUCTION:

- First Generic: Yes.
- Request for Inspection: Yes.
- Reference Product:
  - AMICAR® Tablet, 500 mg, Immunex Corporation
    NDA: 15-197 001
    Rated: No.
  - AMICAR® (aminocaproic acid) acts as an inhibitor of fibrinolysis. It is useful in enhancing hemostasis when fibrinolysis contributes to bleeding (PDR, 1999).
  - AMICAR® is soluble in water, acid and alkaline solutions (PDR, 1999).
  - In adults, oral absorption appears to be a zero-order process with an absorption rate of 5.2 g/hr. The mean lag time in absorption is 10 minutes. After a single oral dose of 5 g, absorption was complete (F=1). Mean ± SD peak plasma concentrations (164 ± 28 ug/mL) were reached within 1.2 ± 0.45 hours (PDR, 1999).
  - After oral administration, the apparent volume of distribution was estimated to be 23.1 ± 6.6 L (mean ± SD). Correspondingly, the volume of distribution after intravenous administration has been reported to be 30.0 ± 8.2 L. After prolonged administration, AMICAR® has been found to distribute throughout extravascular and intravascular compartments of the body, penetrating human red blood cells as well as other tissue cells (PDR, 1999).

- Renal excretion is the primary route of elimination, whether AMICAR® is administered orally or intravenously. Sixty-five percent of the dose is recovered in the urine as unchanged drug and 11% of the dose appears as the metabolite adipic acid. Renal clearance (116 mL/min) approximates endogenous creatinine clearance. The total body clearance is 169 mL/min. The terminal elimination half-life for AMICAR® is approximately 2 hours (PDR, 1999).

- For the treatment of acute bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 10 tablets (5 g) be administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 g) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled (PDR, 1999).

STUDY OBJECTIVE:

The study objective was to determine the bioequivalency of the test product (Aminocaproic Acid Tablet, 500 mg) relative to the marketed reference product (Amicar® Tablet, 500 mg) after administration of equal doses to healthy male subjects under fasting conditions.

STUDY INFORMATION:

SPONSOR:	VERSAPHARM, INC. MARIETTA, GA
SPONSOR'S REPRESENTATIVE:	CLINSITES/CDAI CHARLOTTE, NC
CLINICAL FACILITY:	AAI CLINIC CHAPEL HILL, NC
PRINCIPAL INVESTIGATOR:	JAMES A. LYON, PHARM. D. WILMINGTON, NC
CLINICAL STUDY DATE:	03/27/1998 - 03/29/1998
ANALYTICAL LABORATORY:	

STUDY DIRECTOR:

STATISTICAL ANALYSES:

STUDY DESIGN:

STUDY NO.:	AAI-US-27
PROTOCOL No.:	VER-701
DESIGN TYPE:	CROSSOVER
RANDOMIZED:	Y
NO. OF SEQUENCES:	2
NO. OF PERIODS:	2
NO. OF TREATMENTS:	2
DOSING:	SINGLE, FASTING
WASHOUT PERIOD:	24 HOURS

SUBJECTS:

IRB APPROVAL:	Y
INFORMED CONSENT OBTAINED:	Y
NO. OF SUBJECTS ENROLLED:	24
NO. OF SUBJECTS COMPLETED:	24
VOLUNTEERS:	HEALTHY, MALE
AGE (yrs):	19 - 35
WEIGHT (lbs.):	118 - 233
HEIGHT (inches):	65 - 76

TREATMENT INFORMATION:

TREATMENT ID:	A	B
TEST OR REFERENCE:	T	R
PRODUCT NAME:	AMINOCAPROIC ACID	AMICAR®
MANUFACTURER:	MIKART, INC.	LEDERLE
DISTRIBUTOR:		IMMUNEX
EXPIRATION DATE:	N/A	7/99
STRENGTH:	500 MG	500 MG
DOSAGE FORM:	TABLET	TABLET
LOT NO.:	A980053A	449-362
BATCH SIZE:		N/A
DOSE:	4 TABLETS (2000 MG) WITH 240 ML OF WATER	4 TABLETS (2000 MG) WITH 240 ML OF WATER
STUDY CONDITION:	FASTING	FASTING
LENGTH OF FASTING:	10 HOURS BEFORE AND 4 HOURS POST DOSING	
STANDARDIZED LUNCH:	Y	Y

BLOOD SAMPLES:

Venous blood samples (1x10 mL) were collected before dosing and at the following times post-dose: 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 4.5, 5, and 6 hours. Samples were stored at or below -20° C until shipped to the analytical laboratory for analysis.

STUDY ASSAY INFORMATION:

ANALYTE:	AMINOCAPROIC ACID
ASSAY METHOD:	
MATRIX:	PLASMA
INTERNAL STANDARD:	
UPPER LIMIT OF QUANTITATION:	100.0 UG/ML
LOWER LIMIT OF QUANTITATION:	1.00 UG/ML
SPECIFICITY:	SPECIFIC
SAMPLE STORAGE:	-20° C UNTIL ANALYSIS

Calibration curves were obtained using a weighted ($1/x^2$) least squares regression analysis of the peak area ratios (analyte/internal standard) versus the calibrator concentrations.

PRE-STUDY ASSAY VALIDATION:

Linearity Range: 1.00 - 100 ug/mL
Sensitivity/LOQ: 1.00 ug/mL
Absolute Recovery: Overall mean recovery of Aminocaproic acid from human plasma at 3.0, 30.0, and 80.0 ug/mL was more than or equal to 91.7%. Mean recovery of Internal Standard at 10 ug/mL was 104.6%.
Specific: Yes.
Stability Studies:

a) Aminocaproic acid samples were stable in reconstitution solvent over 168 hours at room temperature (approximately 22° C) and at 4° C.

b) Aminocaproic acid samples were stable in plasma over 48 hours at room temperature (approximately 22° C) and at 4° C.

c) Aminocaproic acid samples were stable over 10 Freeze-Thaw Cycles.

d) The long-term stability study of Aminocaproic acid in frozen plasma samples at -20° C is in progress.

e) The stability studies of stock solutions of Aminocaproic acid and internal standard in progress.

STATISTICAL ANALYSIS:

Statistical data analyses were performed using the SAS GLM Procedure to compare the test and reference products for the pharmacokinetic parameters and the plasma concentrations at each sampling time.

ANOVA and calculation of the 90% confidence interval (CI) were performed on the ln-transformed and un-transformed parameters.

RESULTS:

- Results of the study Standard Curve and Quality Control data are summarized in Table 1.
- Means of the plasma concentrations versus time data for the test and reference products are summarized in Table 2, and are shown graphically in Figure 1.
- Least-Squares Geometric Means, Ratios, RMSEs, and 90% CIs for the ln-transformed pharmacokinetic parameters are demonstrated in Table 3.
- Least-Squares Means, Ratios, RMSEs, and 90% CIs for the un-transformed pharmacokinetic parameters are demonstrated in Table 4.
- Table 5 shows individual percent ratio of AUCT/AUCI for the test product (range: . . .
- Table 6 shows individual percent ratio of AUCT/AUCI for the reference product (range: .
- A statistically significant phase effect ($p < 0.05$) was observed for the ln-transformed Cmax.

- ADVERSE EVENTS:

No serious adverse events were observed. A total of 2 mild adverse events were considered to be possibly related to the study products.

Adverse Event	subject's No	Treatment
Headache	14	B
Nausea	2	A

FORMULATION COMPARISON:

Formulations of the test and reference products are compared in Table 7.

Amounts of Magnesium Stearate and Stearic Acid used in the test product fall in the range reported for oral tablets in the "FDA INACTIVE INGREDIENT GUIDE" (January 1996).

The amount of Povidone used in the test product is similar to that used in a formulation of Etodolac 400 mg tablet (ANDA 74-927).

DISSOLUTION TESTING:

Data from the test and reference products are compared in Table 8. The following method (USP 23) was used:

MEDIUM: Water
VOLUME: 900 mL, 37° ± 0.5° C
APPARATUS: USP 23/NF 18 Apparatus 1, basket
RPM: 100

The dissolution testing data are very similar for the test and reference products. The data pass the USP 23 specifications of "NLT in 45 minutes".

ASSAY POTENCY DATA:

Test product: 100.1%
Reference product: Was not submitted.

CONTENT UNIFORMITY DATA:

MEAN (CV%) Percent Labeled Claim for the Test Product: 100.3% (1.4%), N=30 units

COMMENTS:

1. Twenty-four (24) subjects were enrolled and completed both phases of the study.

2. The pharmacokinetic parameters of ln-transformed AUCT, AUCI, and Cmax meet the 90% CI requirements.

Statistical data analysis performed by the reviewer confirmed the firm's report.

3. The blood samples were collected up to 6 hours, where the plasma values (4.56 - 10.70 ug/mL) were higher than the lower limit of quantitation (1.0 ug/mL).

However, the range of AUCT/AUCinf ratio is for the test product, and for the reference product. Furthermore, the Kels and 6-hour plasma concentrations are similar for the test and reference products for each subject.

4. Chromatograms were submitted for subjects #1-3, 10-12, and 13-15. However, the chromatograms for samples at 5 and 6 hours were not included for these subjects. In addition raw data (peak area ratio) were not submitted for all of the subjects.

The DBE requested an Inspection for this ANDA on 7/1/99, since the firm's product is the First Generic Product of Aminocaproic acid.

5. The firm stated that the reference product was reviewed under Drug Efficacy Study Implementation and was determined to be acceptable for an Abbreviated New Drug Application.

DEFICIENCIES:

1. The firm stated that the long-term stability study of Aminocaproic acid in the frozen plasma samples (stored at -20° C), and the stability studies of stock solutions of Aminocaproic acid and internal standard in (stored are in progress. The firm should submit results of these studies.

2. All of the pre-dose samples for both periods 1 and 2 were re-assayed (pages 353-354 in volume 2 of 5). The reason(s) should be explained.

3. The firm stated that Chromatographic peaks showed sometimes jagged peak shape, due to the acquisition conditions.

The firm should clarify this statement and explain why only some of the chromatographic peaks showed jagged peak shape.

4. Formulas used for calculations of CV%, Accuracy, and Stability data are incorrect (examples: pages 358, 359, and 745 in volume 2 of 5). The corrected data should be submitted.

5. Calculation of %recovery for the internal standard is incorrect (according to the formula provided in page 756, volume 2 of 5). The corrected data should be submitted.

6. Assayed potency data should be submitted for the lot of the reference product used in the bioequivalence study.

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Mikart Inc. on its Aminocaproic Acid Tablets, 500 mg (lot #A980053A) comparing it to 500 mg Amicar® Tablets (lot #449-362) by Immunex (Lederle) has been found incomplete by the Division of Bioequivalence.

2. The dissolution testing data submitted by Mikart Inc. for the test (lot #A980053) and reference (lot #449-362) products have been found acceptable by the Division of Bioequivalence.

3. The firm should be informed of the DEFICIENCIES.

Farahnaz Nouravarsani, 9/15/99

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

RD INITIALED BDAVIT BMD 9/14/99
FT INITIALED BDAVIT Barbara M. Davis 9/15/99

Concur: Dale P. Conner Date: 10/4/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table 1:

STANDARD CURVE DATA (DURING STUDY):

	Conc. (ug/ml)						
	1.00	2.00	5.00	20.0	50.0	90.0	100.0
Mean	1.01	1.93	5.07	20.4	50.7	85.0	103
Accuracy*	101	96.5	101.4	102	101.4	94.4	103
CV%*	3.07	6.06	2.62	2.26	1.40	2.58	3.04
N	12	12	12	12	12	12	12

*: The reviewer calculated the Accuracy and CV%.

QUALITY CONTROL DATA (DURING STUDY):

	Conc. (ug/ml)		
	3.00	30.0	80.0
Mean	3.28	29.9	78.4
Accuracy*	109	99.7	98.0
CV%*	8.35	4.58	4.23
N	24	24	24

*: The reviewer calculated the Accuracy and CV%.

Table 2:

MEAN (CV%) PLASMA CONCENTRATIONS, UG/ML, N = 24:

Time Hr	Treatment A TEST	Treatment B REFERENCE
0.00	0.00 (----)	0.00 (----)
0.50	28.4 (42.8)	30.4 (40.6)
0.67	44.7 (29.2)	43.7 (27.9)
0.83	53.6 (21.5)	51.2 (20.3)
1.00	56.7 (18.3)	53.5 (15.0)
1.25	54.5 (15.2)	52.7 (14.2)
1.50	50.3 (12.7)	49.2 (13.5)
1.75	46.0 (12.9)	44.3 (13.2)
2.00	40.6 (12.6)	40.4 (15.8)
2.50	32.1 (13.6)	31.8 (16.9)
3.00	25.1 (15.4)	25.3 (18.2)
4.00	16.1 (18.3)	15.9 (19.0)
4.50	12.6 (18.2)	12.7 (20.7)
5.00	10.2 (23.1)	9.93 (21.8)
6.00	6.79 (23.2)	6.84 (22.9)

Table 3:

LEAST-SQUARES GEOMETRIC MEAN FOR LN-TRANSFORMED DATA, RATIO, RMSE, AND 90% CI, N = 24:

Parameter	TEST	REF.	RATIO	RMSE	90%CI
AUCT hr*ug/ml	153.6	151.9	1.011	0.023	1.000-1.023
AUCI hr*ug/ml	168.5	166.9	1.009	0.024	0.998-1.021
Cmax ug/mL	57.22	55.33	1.034	0.066	1.001-1.069

Table 4:

LEAST-SQUARES MEAN, RATIO, RMSE, AND 90% CI, N = 24:

Parameter	TEST	REF.	RATIO	RMSE	90%CI
AUCT hr*ug/ml	154.7	152.9	1.012	3.65	1.000-1.024
AUCI hr*ug/ml	169.9	168.2	1.010	4.07	0.998-1.022
Cmax ug/mL	58.03	55.84	1.039	4.11	1.003-1.076
Tmax hr	1.06	1.05	1.011		
kel 1/hr	0.4603	0.4583	1.004		
T(1/2) hr	1.52	1.52	0.997		

Table 5:

PERCENT RATIO OF AUCT/AUCI FOR THE TEST PRODUCT:

Subject	AUCT	AUCI	AUCT/AUCI%
1	140.293	163.416	85.9
2	166.397	181.596	91.6
3	168.879	192.077	87.9
4	146.275	161.236	90.7
5	135.065	146.665	92.1
6	140.960	158.068	89.2
7	164.773	180.366	91.4
8	168.609	187.284	90.0
9	161.167	170.960	94.3
10	148.243	161.150	92.0
11	130.968	141.329	92.7
12	159.390	170.110	93.7
13	197.316	218.201	90.4
14	170.371	182.156	93.5
15	143.949	156.214	92.1
16	158.507	174.692	90.7
17	140.153	151.623	92.4
18	125.914	134.754	93.4
19	141.050	156.504	90.1
20	136.223	149.166	91.3
21	167.038	195.071	85.6
22	134.339	146.036	92.0
23	161.654	172.268	93.8
24	206.195	227.210	90.8
Range:			85.6-94.3

Table 6:

PERCENT RATIO OF AUCT/AUCI FOR THE REFERENCE PRODUCT:

Subject	AUCT	AUCI	AUCT/AUCI%
	136.743	158.649	86.2
	169.749	187.889	90.3
	169.012	187.117	90.3
	147.459	161.495	91.3
	130.043	141.142	92.1
	137.351	153.897	89.2
	161.348	178.788	90.2
	168.906	186.173	90.7
	155.820	164.225	94.9
	153.028	168.483	90.8
	130.902	141.259	92.7
	160.579	173.793	92.4
	182.586	202.107	90.3
	164.427	176.315	93.3
	144.928	157.603	92.0
	147.288	166.927	88.2
	137.727	150.761	91.4
	135.406	144.287	93.8
	139.618	158.024	88.4
	136.029	148.404	91.7
	165.914	191.508	86.6
	135.769	145.709	93.2
	151.829	162.879	93.2
	207.039	228.603	90.6
nge:			86.2-94.9

Table 7:

FORMULATION COMPARISON OF THE TEST AND REFERENCE PRODUCTS:

INGREDIENTS	TEST mg/Tablet	REFERENCE mg/Tablet
AMINOCAPROIC ACID USP	500	500
POVIDONE		
STEARIC ACID		
MAGNESIUM STEARATE		

Table 8:

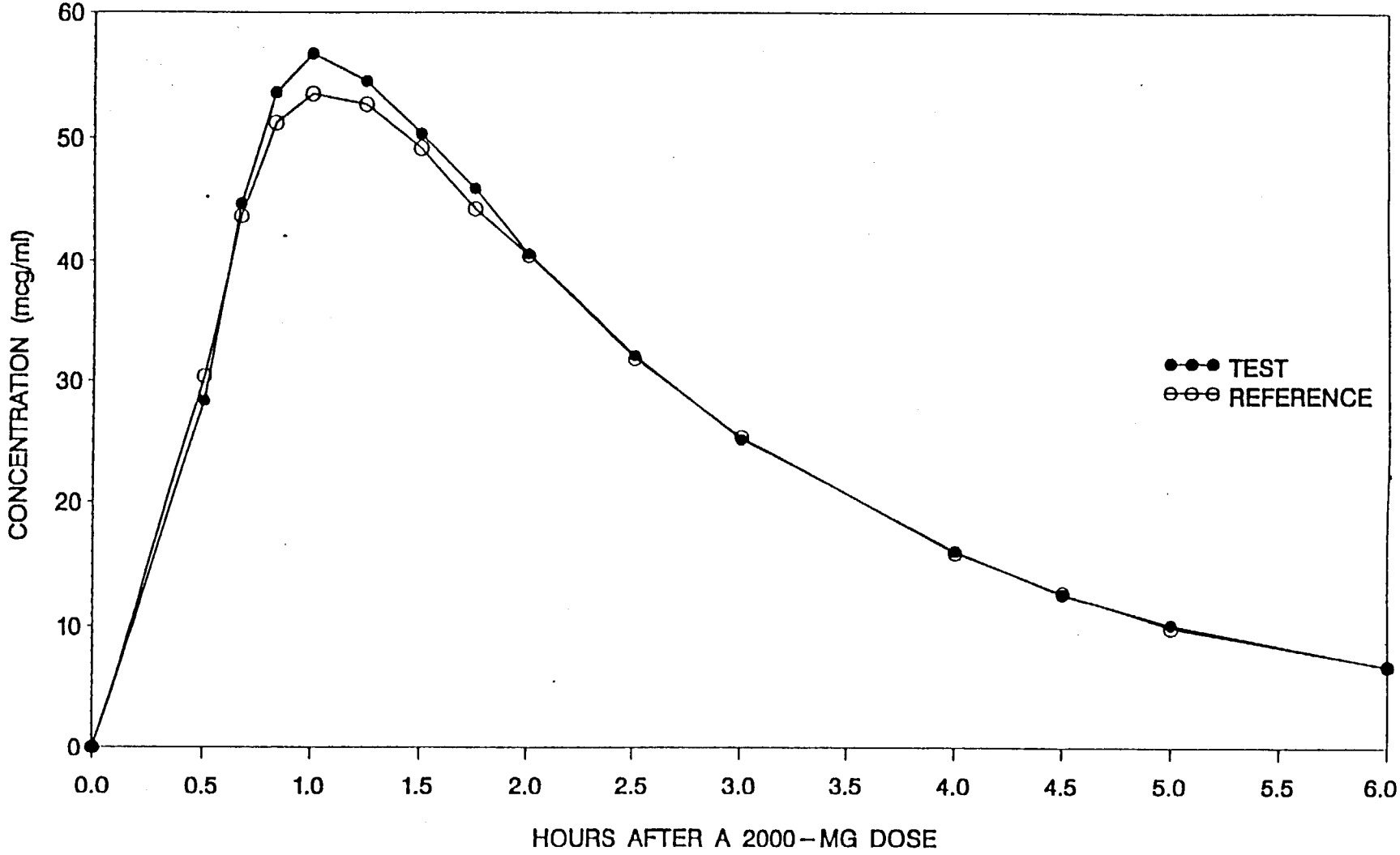
IN-VITRO DISSOLUTION TESTING:

DRUG (GENERIC NAME):	AMINOCAPROIC ACID TABLETS
STRENGTH:	500 MG
FIRM:	MIKART INC.
REFERENCE PRODUCT:	AMICAR® TABLETS, 500 MG
METHOD:	**USP 23**
DISSOLUTION MEDIUM:	WATER AT 37° ± 0.5° C
VOLUME:	900 ML
DISSOLUTION APPARATUS:	USP 23 APPARATUS 1 (BASKET)
RPM:	100 RPM
N:	12
SPECIFICATIONS:	**NLT IN 45 MINUTES**
SIMILARITY FACTOR (F2):	**79.14**

	Test Product Lot #A980053 Test Date: 3/24/98		Reference Product: Lot #449-362 Test Date: 3/24/98	
Time (min)	Strength (mg) 500		Strength (mg) 500	
	MEAN	RANGE	MEAN	RANGE
15.00	101.1		99.8	
30.00	101.2		99.3	
45.00	102.8		99.3	
60.00	101.3		98.9	

Figure 1

AMINOCAPROIC ACID STUDY AAI-US-27
PROTOCOL VER-701
Least-Squares Mean Plasma Concentrations (N=24)



BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-602 APPLICANT: Mikart Inc.

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 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. You stated that the long-term stability study of Aminocaproic acid in the frozen plasma samples (stored at -20° C), and the stability studies of stock solutions of Aminocaproic acid and internal standard in) are in progress. Please submit results of these studies.

2. All of the pre-dose samples for both periods 1 and 2 were re-assayed (pages 353-354 in volume 2 of 5). The reason(s) should be explained.

3. You stated that Chromatographic peaks showed sometimes jagged peak shape, due to the acquisition conditions.

Please clarify this statement and explain why only <u>some</u> of the chromatographic peaks showed jagged peak shape.

4. Formulas used for calculations of CV%, Accuracy, and Stability data are incorrect (examples: pages 358, 359, and 745 in volume 2 of 5). The corrected data should be submitted.

5. Calculation of %recovery for the internal standard is incorrect (according to the formula provided in page 756, volume 2 of 5). The corrected data should be submitted.

6. Assayed potency data should be submitted for the lot of the reference product used in the bioequivalence study.

Sincerely yours,

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