CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-602

APPROVAL LETTER

ANDA 75-602

MAY 24 2001

Mikart, Inc.
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318

Dear Madam:

This is in reference to your abbreviated new drug application dated March 17, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Aminocaproic Acid Tablets USP, 500 mg.

Reference is also made to your amendments dated March 21, April 28, and October 25, 2000; and January 31 and February 8, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Aminocaproic Acid Tablets USP, 500 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Amicar® Tablets, 500 mg, of Immunex Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 5/24/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-602

APPROVED DRAFT LABELING

NDC 61748-045-01

APPROVED

Aminocaproic Acid
Tablets USP 500 mg

Each tablet contains:
Aminocaproic Acid..... 500 mg

Rx only

Contents: 100 Tablets

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight container with a child-resistant closure.

Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (see USP).

USUAL DOSAGE: See package insert for full prescribing information.

WARNING: Keep this and all drugs out of the reach of children.

Manufactured by: MIKART, INC.
Atlanta, GA 30318

Marketed by: VersaPharm Incorporated
Marietta, GA 30062-1509

Code 731A10

Rev. 08/00

61748045

Aminocaproic Acid Tablets USP

500 mg

℞ only

Rev. 08/00 Code 731A00

APPROVED

MAY 24 2001

DESCRIPTION:
Aminocaproic acid is 6-amino-hexanoic acid, which acts as an inhibitor of fibrinolysis.

Its structural formula is:

$C_6H_{13}NO_2$ M.W. 131.17

Aminocaproic acid is soluble in water, acid, and alkaline solutions; it is sparingly soluble in methanol and practically insoluble in chloroform.

Each Aminocaproic Acid Tablet USP for oral administration contains 500 mg of aminocaproic acid and the following inactive ingredients: magnesium stearate, povidone and stearic acid.

CLINICAL PHARMACOLOGY:
The fibrinolysis-inhibitory effects of aminocaproic acid appear to be exerted principally via inhibition of plasminogen activators and to a lesser degree through antiplasmin activity.

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 mcg/mL) were reached within 1.2 ± 0.45 hours.

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, aminocaproic acid has been found to distribute throughout extravascular and intravascular compartments of the body, penetrating human red blood cells as well as other tissue cells.

Renal excretion is the primary route of elimination, whether aminocaproic acid 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 aminocaproic acid is approximately 2 hours.

INDICATIONS AND USAGE:
Aminocaproic Acid Tablets USP are useful in enhancing hemostasis when fibrinolysis contributes to bleeding. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as aplastic anemia; abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung,

hemostatic [illegible] contributes to bleeding. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as aplastic anemia; abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is surgical hematuria (following prostatectomy and nephrectomy) or nonsurgical hematuria (accompanying polycystic or neoplastic diseases of the genitourinary system). (See **WARNINGS**.)

CONTRAINDICATIONS:
Aminocaproic acid should not be used when there is evidence of an active intravascular clotting process.

When there is uncertainty as to whether the cause of bleeding is primary fibrinolysis or disseminated intravascular coagulation (DIC), this distinction must be made before administering aminocaproic acid.

The following tests can be applied to differentiate the two conditions:

•Platelet count is usually decreased in DIC but normal in primary fibrinolysis.

•Protamine paracoagulation test is positive in DIC; a precipitate forms when protamine sulphate is dropped into citrated plasma. The test is negative in the presence of primary fibrinolysis.

•The euglobulin clot lysis test is abnormal in primary fibrinolysis but normal in DIC. Aminocaproic acid must not be used in the presence of DIC without concomitant heparin.

WARNINGS:
In patients with upper urinary tract bleeding, aminocaproic acid administration has been known to cause intrarenal obstruction in the form of glomerular capillary thrombosis or clots in the renal pelvis and ureters. For this reason, aminocaproic acid should not be used in hematuria of upper urinary tract origin, unless the possible benefits outweigh the risk.

Subendocardial hemorrhages have been observed in dogs given intravenous infusions of 0.2 times the maximum human therapeutic dose of aminocaproic acid and in monkeys given 8 times the maximum human therapeutic dose of aminocaproic acid.

Fatty degeneration of the myocardium has been reported in dogs given intravenous doses of aminocaproic acid at 0.8 to 3.3 times the maximum human therapeutic dose and in monkeys given intravenous doses of aminocaproic acid at 6 times the maximum human therapeutic dose.

Rarely, skeletal muscle weakness with necrosis of muscle fibers has been reported following prolonged administration. Clinical presentation may range from mild myalgias with weakness and fatigue to a severe proximal myopathy with rhabdomyolysis, myoglobinuria, and acute renal failure. Muscle enzymes, especially creatine phosphokinase (CPK) are elevated. CPK levels should be monitored in patients on long-term therapy. Aminocaproic acid administration should be stopped if a rise in CPK is noted. Resolution follows discontinuation of aminocaproic acid; however, the syndrome may recur if aminocaproic acid is restarted.

The possibility of cardiac muscle damage should also be considered when skeletal myopathy occurs. One case of cardiac and hepatic lesions observed in man has been reported. The patient received 2 g of aminocaproic acid every 6 hours for a total dose of 26 g. Death was due to continued cerebrovascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

PRECAUTIONS:
General:
Aminocaproic acid inhibits both the action of plasminogen activators and to a lesser

3

[illegible] urinary tract origin unless the possible benefits outweigh the risk.

Subendocardial hemorrhages have been observed in dogs given intravenous infusions of 0.2 times the maximum human therapeutic dose of aminocaproic acid and in monkeys given 3 times the maximum human therapeutic dose of aminocaproic acid.

Fatty degeneration of the myocardium has been reported in dogs given intravenous doses of aminocaproic acid at 0.8 to 3.3 times the maximum human therapeutic dose and in monkeys given intravenous doses of aminocaproic acid at 6 times the maximum human therapeutic dose.

Rarely, skeletal muscle weakness with necrosis of muscle fibers has been reported following prolonged administration. Clinical presentation may range from mild myalgias with weakness and fatigue to a severe proximal myopathy with rhabdomyolysis, myoglobinuria, and acute renal failure. Muscle enzymes, especially creatine phosphokinase (CPK) are elevated. CPK levels should be monitored in patients on long-term therapy. Aminocaproic acid administration should be stopped if a rise in CPK is noted. Resolution follows discontinuation of aminocaproic acid; however, the syndrome may recur if aminocaproic acid is restarted.

The possibility of cardiac muscle damage should also be considered when skeletal myopathy occurs. One case of cardiac and hepatic lesions observed in man has been reported. The patient received 2 g of aminocaproic acid every 6 hours for a total dose of 26 g. Death was due to continued cerebrovascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

PRECAUTIONS:

General:

Aminocaproic acid inhibits both the action of plasminogen activators and, to a lesser degree, plasmin activity. The drug should NOT be administered without a definite diagnosis and/or laboratory finding indicative of hyperfibrinolysis (hyperplasminemia).[1]

Inhibition of fibrinolysis by aminocaproic acid may theoretically result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of intravascular clotting which followed this treatment. Rather, it appears that such intravascular clotting was most likely due to the patient's preexisting clinical condition, e.g., the presence of DIC. It has been postulated that extravascular clots formed in vivo may not undergo spontaneous lysis as do normal clots.

Reports have appeared in the literature of an increased incidence of certain neurological deficits such as hydrocephalus, cerebral ischemia, or cerebral vasospasm associated with the use of antifibrinolytic agents in the treatment of subarachnoid hemorrhage (SAH). All of these events have also been described as part of the natural course of SAH, or as a consequence of diagnostic procedures such as angiography. Drug relatedness remains unclear.

Epsilon-aminocaproic acid should not be administered with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

Laboratory Tests:

The use of aminocaproic acid should be accompanied by tests designed to determine

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-602

CHEMISTRY REVIEW(S)

AUG 14 2000

38. Chemistry comments to be provided to the applicant

ANDA: **75-602** APPLICANT: **Mikart, Incorporated**

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 500 mg

The following deficiencies represent MINOR deficiencies:

1. DMF is deficient and the holder has been informed.

2. Your specification for in the drug substance is too high compared to your specification for in the finished product and stability specifications.

3. What do you mean by completion of Pharmacy step? Is it the end of weighing of ingredients? Note that start time of manufacturing is the day the active ingredient is mixed with other ingredients.

4. We acknowledge the receipt of your in-process summary production (p 10 of Amendment dated March 21, 2000) and that friability, disintegration, and individual weight variations of 20 units have been removed from the tablet compression master. Please clarify.

5. Please refer to question #5 in the last deficiency letter and clarify if the actual test dates for the 30-day and 60-day time stations are July 24 and July 26, 1996, respectively. Note that scheduled removal date for 30-day and 60-day time stations are June 24 and July 25, 1996, respectively.

6. We acknowledge that the test for related substances was added on the 29th of July 1998. However, no test was conducted at the 36 months time station (April 16, 1999) for lot #B960222. Please explain. In addition, your stability report form should have all the changes such as moisture and specifications for related substances.

Sincerely yours,

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW # 2

2. ANDA # 75-602

3. NAME AND ADDRESS OF APPLICANT
Mikart, Incorporated
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Amicar® Tablets, 500 mg (NDA #15-197). There are no patent information and exclusivity period for the listed drug (pp 12, 14).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Aminocaproic Acid

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 17, 1999: Original Submission
April 28, 1999: Refuse to File
May 14, 1999: Amendment
May 17, 1999: Acceptable for Filing
October 4, 1999: Bio Review #1
October 29, 1999: Chemistry Review #1
November 1, 1999: Labeling Review #1
March 21, 2000: Amendment

10. PHARMACOLOGICAL CATEGORY
Antifibrinolytic Agent

11. ℞ or OTC
℞

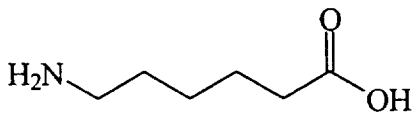
12. RELATED DMFs

13. DOSAGE FORM
Tablet

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE

Aminocaproic Acid. $C_6H_{13}NO_2$. 131.18. 6-Aminohexanoic acid



16. RECORDS AND REPORTS
N/A

17. COMMENTS
New comments/deficiencies are in bold.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, MINOR

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
July 26, 2000

Page(s) 16

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Commercial/Confidential

Information and are not

releasable.

Chem Rev 2

7/26/00

38. Chemistry comments to be provided to the applicant

ANDA: **75-602** APPLICANT: **Mikart, Incorporated**

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 500 mg

The following deficiencies represent MINOR deficiencies:

1. DMF is deficient and the holder has been informed.

2. Your specification for in the drug substance is too high compared to your specification for in the finished product and stability specifications.

3. What do you mean by completion of Pharmacy step? Is it the end of weighing of ingredients? Note that start time of manufacturing is the day the active ingredient is mixed with other ingredients.

4. We acknowledge the receipt of your in-process summary production (p 10 of Amendment dated March 21, 2000) and that friability, disintegration, and individual weight variations of 20 units have been removed from the tablet compression master. Please clarify.

5. Please refer to question #5 in the last deficiency letter and clarify if the actual test dates for the 30-day and 60-day time stations are July 24 and July 26, 1996, respectively. Note that scheduled removal date for 30-day and 60-day time stations are June 24 and July 25, 1996, respectively.

6. We acknowledge that the test for related substances was added on the 29th of July 1998. However, no test was conducted at the 36 months time station (April 16, 1999) for lot #B960222. Please explain. In addition, your stability report form should have all the changes such as moisture and specifications for related substances.

Sincerely yours,

Vilayat Sayed 8/14/00

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV · 1 1999

38. Chemistry comments to be provided to the applicant

ANDA: **75-602** APPLICANT: **Mikart, Incorporated**

DRUG PRODUCT: Aminocaproic Acid Tablets USP, 500 mg

The following deficiencies represent MAJOR deficiencies.

A. Deficiencies:

1. What is the time limit of your manufacturing process?

2. Reported hardness results for both executed batches are in the range of Please reduce your specified hardness range to reflect results obtained. In addition, correct your blank batch record to reflect the change in the lower limit from .

3. Please include an organoleptic test in your finished product specifications. Also, we require tests and specifications for moisture and hardness in your finished product specifications.

4. We note that in your method validation report for the analysis of you established a limit of NMT . Please include this limit in your finished product and stability specifications.

5. Please clarify the actual test dates for your accelerated stability data (p. 2052) and resubmit your stability data with the correct dates.

6. We acknowledge that you added a test for related substances in July 1998 and at the 6 and 9 months stations (lot #A980053) no related substance was detected We recommend that you reduce your limits for individual and total related substances because the current specifications are too broad compared to results obtained during your validation studies. Also, please specify on both your finished product and stability specifications, "Limit for individual related substances, excluding caprolactam."

7. Please submit updated room temperature stability data.

8. We note that you increased the upper limit of your hardness range from to accommodate your accelerated stability data for lot #B960222 . Room temperature hardness results for the same lot are from

s). Do you have an explanation for the high hardness values obtained during accelerated stability studies of lot #B960222 (p. 2052)?

9. Please include a test and specification for moisture in your stability specifications.

10. How did you calculate your expiration period?

11. Purified water and total weight should be included in Components/Composition statement. Please revise and resubmit.

B. In addition to responding to the deficiencies presented above, please include the primary function of each excipient in the component/composition statement.

Sincerely yours,

Vilayat Sayed

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW # 1

2. ANDA # 75-602

3. NAME AND ADDRESS OF APPLICANT
Mikart, Incorporated
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Amicar® Tablets, 500 mg (NDA #15-197). There are no patent information and exclusivity period for the listed drug (pp 12, 14).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Aminocaproic Acid

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 17, 1999: Original Submission
April 28, 1999: Refuse to File
May 14, 1999: Amendment
May 17, 1999: Acceptable for Filing

10. PHARMACOLOGICAL CATEGORY
Antifibrinolytic Agent

11. ℞ or OTC
℞

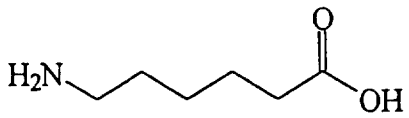
12. RELATED DMFs

13. DOSAGE FORM
Tablet

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE

Aminocaproic Acid. $C_6H_{13}NO_2$. 131.18. 6-Aminohexanoic acid



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See review

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, Major.

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
October 27, 1999

Page(s) 13

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Information and are not

releasable.

chem 1

10/22/99

1. CHEMISTRY REVIEW # 3

2. ANDA # 75-602

3. NAME AND ADDRESS OF APPLICANT
Mikart, Incorporated
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Amicar® Tablets, 500 mg (NDA #15-197). There are no patent information and exclusivity period for the listed drug (pp 12, 14).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Aminocaproic Acid

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 17, 1999: Original Submission
April 28, 1999: Refuse to File
May 14, 1999: Amendment
May 17, 1999: Acceptable for Filing
October 4, 1999: Bio Review #1
October 29, 1999: Chemistry Review #1
November 1, 1999: Labeling Review #1
March 21, 2000: Amendment
August 11, 2000: Labeling Review #2
August 11, 2000: Chemistry Review #2
September 5, 2000: Bioequivalence Audit by Div. Of Scientific Investigations
October 25, 2000: Amendment

10. PHARMACOLOGICAL CATEGORY
Antifibrinolytic Agent

11. ℞ or OTC
℞

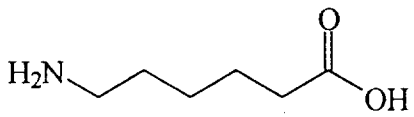
12. RELATED DMFs

13. DOSAGE FORM
Tablet

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE

Aminocaproic Acid. $C_6H_{13}NO_2$. 131.18. 6-Aminohexanoic acid



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See review

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable pending labeling and bioequivalence.

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
November 7, 2000

Page(s) 19

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Chem Rev #3

11/7/00

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, [illegible] (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 [illegible] 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 [illegible] boratory should be forwarded to both divisions of the Agency.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 12/18/2000

Concur: Barbara M Davit Date: 12/22/00

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 David

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 <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.

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 9/15/99
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:

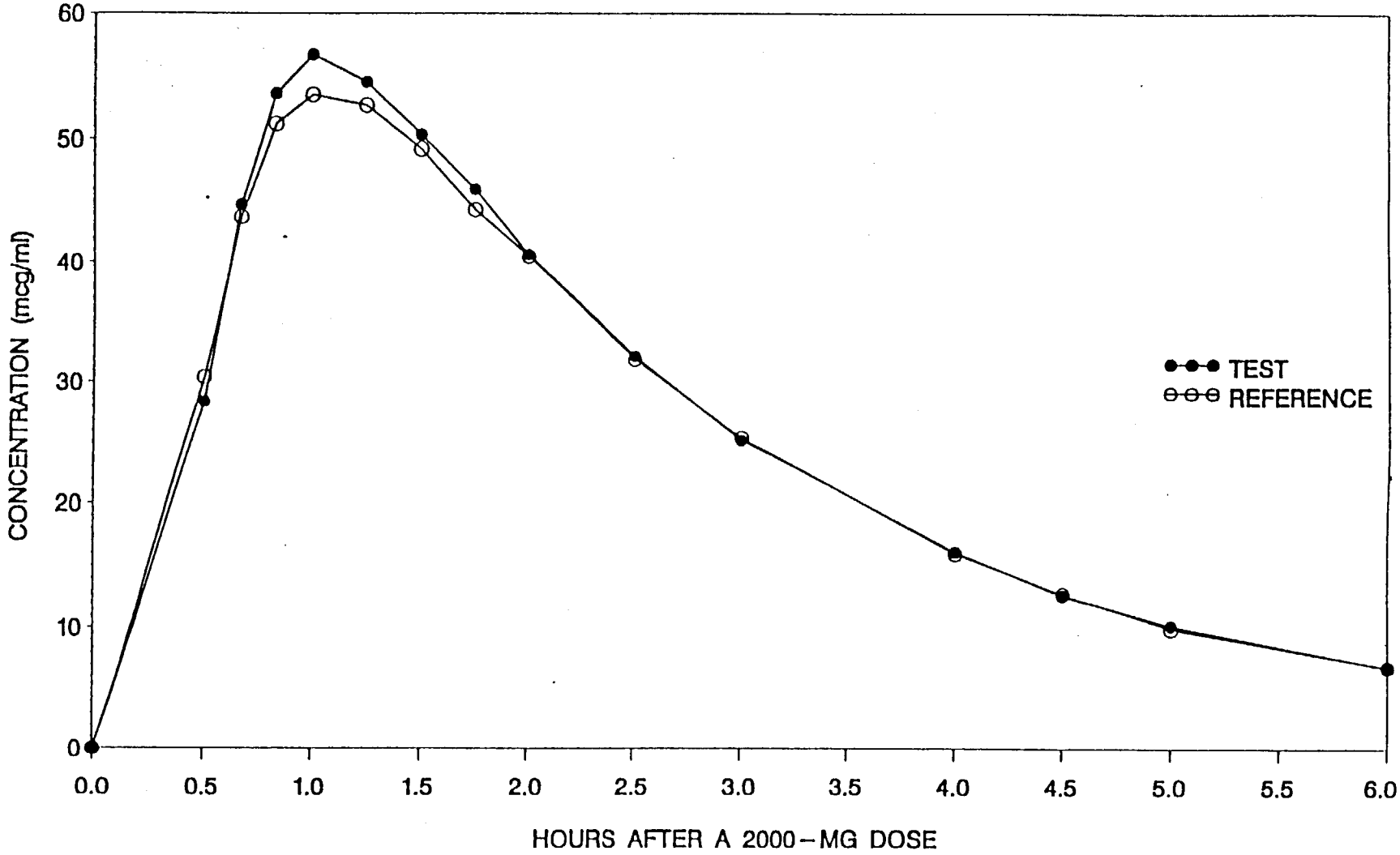
IN-VITRO DISSOLUTION TESTING:

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-602

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-602 Date of Submission: March 21, 2000

Applicant's Name: Mikart, Inc.

Established Name: Aminocaproic Acid Tablets USP, 500 mg

Labeling Deficiencies:

INSERT

a. PRECAUTIONS

i. General

Replace the last paragraph with the following.

Epsilon-aminocaproic acid should not be administered with Factor IX Complex concentrates or Anti-Inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

ii. Pregnancy

Delete "Tablets USP" from the second sentence.

b. ADVERSE REACTIONS (Special Senses)

Capitalize the "t" in "tinnitus" for consistency.

Please revise your insert labeling as instructed above and submit 12 final printed copies of container label and package insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-602 Date of Submission: March 21, 2000

Applicant's Name: Mikart, Inc.

Established Name: Aminocaproic Acid Tablets USP, 500 mg

Labeling Deficiencies:

INSERT

a. PRECAUTIONS

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Replace the last paragraph with the following.

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Capitalize the "t" in "tinnitus" for consistency.

Please revise your insert labeling as instructed above and submit 12 final printed copies of container label and package insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling?
- Container Labels:
- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

• Was this approval based upon a petition?	No
• What is the RLD on the 356(h) form:	Amicar
• NDA Number:	15-197
• NDA Drug Name:	Amicar
• NDA Firm:	Immunex Corporation
• Date of Approval of NDA Insert and supplement #:	April 3, 2000; S-034
• Has this been verified by the MIS system for the NDA?	YES
• Was this approval based upon an OGD labeling guidance?	NO
• Basis of Approval for the Container Labels:	Side by Side

FOR THE RECORD:

1. Model Labeling – Amicar, Immunex Corporation, NDA 15-197/S-034, Approved April 3, 2000.

2. Patents/Exclusivities – There are no patents or exclusivities listed in the 19th Edition of the Orange Book.

3. Container/Closure – HDPE bottle with CRC

4. Storage/Dispensing Recommendations
   - USP: Preserve in tight containers.
   - NDA: Store between 15^0-30^0C (59^0-86^0F), Dispense in tight containers.
   - ANDA: Store at controlled room temperature, 15^0-30^0C (59^0-86^0F), Dispense in a tight container with a child-resistant closure.

5. Outside firms are used for product testing only.

6. Component/Composition – Consistent, see page 32.

7. Potential FIRST GENERIC.

8. Description – consistent with application, see page 1715.

9. HOW SUPPLIED section: Firm's statement, "Aminocaproic Acid Tablets USP, which contain aminocaproic acid 500 mg" appears redundant however, it is acceptable. It is the reviewer's opinion that it should read as, "Aminocaproic Acid Tablets USP, 500 mg for oral administration are supplied as..."

Date of Review: August 8, 2000	Date of Submission: March 21, 2000
Primary Reviewer: Koung Lee	Date: 8/11/00
Team Leader: Charlie Hoppes	Date: 8/11/00

cc.

LABELING

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-602

Date of Submission: March 17, 1999
Refuse to file date: April 28, 1999
Filing date: May 17, 1999

Applicant's Name: Mikart, Inc.

Established Name: Aminocaproic Acid Tablets USP, 500 mg

Labeling Deficiencies:

1. CONTAINER

   Add "(see USP)" after the storage temperature statement.

2. INSERT

   a. DESCRIPTION

      i. Replace "chemical" with "structural" in the second sentence.

      ii. Replace "M.W. 131.18" with "M.W. 131.17"

   b. PRECAUTIONS

      Add as the last paragraph the following.

      > Thrombosis with severe sequelae (acute myocardial infarction, gangrene) has been rarely reported in patients with hemophilia receiving combined treatment with Factor IX concentrate and aminocaproic acid. Aminocaproic acid should not be administered concomitantly with prothrombin complex concentrates or with activated prothrombin concentrates unless the increased risk of thrombosis is outweighed by the anticipated clinical benefit.

   c. ADVERSE REACTIONS (Urogenital)

      i. Delete "ejaculatory disorder" from the first sentence.

      ii. Add "been" between "These have" and "reported to date".

      iii. Add "of completion" between "24 to 48 hours" and "of therapy."

   d. OVERDOSAGE

      Delete the comma between "tumor and seizures" and "experienced seizures after".

   e. HOW SUPPLIED

      See CONTAINER comment.

Please revise your label and labeling as instructed above and submit 12 final printed copies of container label and package insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling?
- Container Labels:
- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

• Was this approval based upon a petition?	No
• What is the RLD on the 356(h) form:	Amicar
• NDA Number:	15-197
• NDA Drug Name:	Amicar
• NDA Firm:	Immunex Corporation
• Date of Approval of NDA Insert and supplement #:	March 3, 1998, S-030
• Has this been verified by the MIS system for the NDA?	YES
• Was this approval based upon an OGD labeling guidance?	NO
• Basis of Approval for the Container Labels:	Side by Side

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?	x		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

FOR THE RECORD:

1. Model Labeling – Amicar, Immunex Corporation, NDA 15-197/S-030, Approved April16, 1997.

2. Patents/Exclusivities – There are no patents or exclusivities listed in the 19th Edition of the Orange Book.

3. Container/Closure – HDPE bottle with CRC

4. Storage/Dispensing Recommendations
   - USP: Preserve in tight containers.
   - NDA: Store between 15^0-30^0C (59^0-86^0F), Dispense in tight containers.
   - ANDA: Store at controlled room temperature, 15^0-30^0C (59^0-86^0F), Dispense in a tight container with a child-resistant closure.

5. Outside firms are used for product testing only.

6. Component/Composition – Consistent, see page 32.

7. Potential FIRST GENERIC.

8. Description – consistent with application, see page 1715.

9. HOW SUPPLIED section: Firm's statement, "Aminocaproic Acid Tablets USP, which contain aminocaproic acid 500 mg" appears redundant however, it is acceptable. It is the reviewer's opinion that it should read as, "Aminocaproic Acid Tablets USP, 500 mg for oral administration are supplied as..."

Date of Review: October 29, 1999

Date of Submission: March 17, 1999
Refuse to file date: April 28, 1999
Filing date: May 17, 1999

Primary Reviewer: Koung Lee

Date: 11/1/99

Team Leader: Charlie Hoppes

Date: 11/1/99

cc:

ELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-602

CORRESPONDENCE

Mikart

mtd KS
10/31/00

October 25, 2000

ORIG AMENDMENT
N|AM

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

RE: ANDA 75-602
Aminocaproic Acid Tablets USP, 500 mg

MINOR AMENDMENT
Responses to Chemistry and Labeling Deficiencies

Dear Sir/Madam:

Reference is made to the Agency's August 14, 2000 Not Approvable Letter to the above listed application. Reference is also made to Mikart, Inc.'s abbreviated new drug application dated March 17, 1999 and to the MAJOR amendment to the application dated March 21, 2000.

Mikart, Inc. herein submits a full and complete response to all items listed in the Not Approvable Letter. To assist in the review of this submission, all Agency comments are reprinted in full and in bold type, with the sponsor's point-by-point responses following. For additional reference, a copy of the Agency's Not Approvable Letter, dated August 14, 2000, is also included.

Thank you for your cooperation in the review of this material. If you have any questions or concerns regarding this submission please contact Andrew Kluessendorf, Manager, Regulatory Submissions at (404) 355-3343.

Sincerely,

Cerie B. McDonald
President

CENTER FOR DRUG
REC'D
OCT 26 2000
OGD
EVALUATION AND RESEARCH

10/24/00

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432

Mikart

January 31, 2001

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AF

RE: ANDA 75-602
Aminocaproic Acid Tablets USP, 500 mg

FINAL PRINTED LABELING

Dear Sir/Madam:

Reference is made to the Agency's January 9, 2001 Labeling Deficiency facsimile to the above listed application. Reference is also made to Mikart, Inc.'s abbreviated new drug application dated March 17, 1999 and to amendments to the application dated March 21, 2000 and October 25, 2000.

Mikart, Inc. herein submits final printed copies of labels and labeling. The archival copy of this submission contains one (1) copy of the final printed labeling. The working copy contains twelve (12) copies of the final printed labeling. To assist in the review of this submission, a copy of the Agency's facsimile, dated January 9, 2001, is also included.

Thank you for your cooperation in the review of this material. If you have any questions or concerns regarding this submission please contact Andrew Kluessendorf, Manager, Regulatory Submissions at (404) 355-3343.

Sincerely,

Cerie B. McDonald
President

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB - 1 2001
OGD

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432

Mikart

March 21, 2000

NDA ORIG AMENDMENT
N/AC

Mr. Douglas Sporn, Director
Office of Generic Drugs
Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 75-602 Aminocaproic Acid Tablets USP 500 mg
MAJOR AMENDMENT TO AN UNAPPROVED APPLICATION

Dear Mr. Sporn:

This letter is in response to the deficiency letter dated November 1, 1999 regarding the aforementioned application. We would like to respond now to the issues raised. Please see the attached pages for both the agency comment and the Mikart response.

With the submission of this information, Mikart, Inc. trusts that there are no longer any outstanding deficiencies. Thank you for your cooperation in the review of this material. Please feel free to contact us should you require any additional information.

Sincerely,

Cerie B. McDonald
President

CBM/sw

Attachments

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432

ANDA 75-602

Mikart, Inc.
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318-2112

JUN 23 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated April 28, 1999 and your amendment May 14, 1999.

NAME OF DRUG: Aminocaproic Acid Tablets USP, 500 mg

DATE OF APPLICATION: March 17, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 17, 1999

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

Harvey A Drearlong
for

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Mikart

Ack for filing
S. Middleton 6/15/99
505 (j)(2)(A)

BIOAVAILABILITY

May 14, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
Room 150
7500 Standish Place
Rockville, MD 20857-2773

ORIG AMENDMENT

N/AC

Re: ANDA #75-602 for Aminocaproic Acid Tablets USP 500 mg
Supplement to an unapproved application

Dear Mr. Sporn:

Mikart, Inc. would like to respond to the refusal to file letter dated April 28, 1999 regarding Aminocaproic Acid Tablets USP 500 mg. Please refer to the attached documents as supporting evidence for the bioequivalency study, including; pre-screening of patients, consent forms, medical records, clinical raw data and test article inventory. Also, a diskette in ASCII format containing pertinent pharmacokinetic data is included.

Accelerated stability was performed on batch B960222 and is included in the original submission. Accelerated stability was not performed on batch A980053 because it is Mikart's policy to perform accelerated stability only on the first batch of each formula. Additional accelerated stability studies are only performed when there is a change in the manufacturing formula, manufacturing or packaging procedures, or packaging components. ~~Batch A980053 was manufactured and packaged under similar conditions as batch B960222.~~ Please note that both batches are under long term ambient stability studies.

The master packaging instructions were included in the original submission on pages 1191-1206 for batch A980053 and pages 1428-1439 for batch B960222. Packaging reconciliation sheets for B960222 was included on page 1439 but was inadvertently omitted for A980053. The packaging reconciliation sheets are included herein.

Should you have any questions, please contact me at (404)-351-4510. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 17 1999
OGD

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432

ANDA 75-602

Mikart, Inc.
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318-2112

APR 28 1999

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated March 17, 1999 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Aminocaproic Acid Tablets USP, 500 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

Regarding the bioequivalence study, the following items have not been submitted in the study results:

- Pre-screening of patients
- Consent Forms
- Medical Records
- Clinical Raw Data
- Test Article Inventory

You have failed to provide 3 month accelerated stability data required to request a 24-month expiration date for batch A980053. We refer you to Policy and Procedure Guide 32-92.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Please submit a diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses. For each study, two separate files should be configured as follows:

(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$;...

(b) subj seq per trt C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

Also, please provide a packaging reconciliation summary for the test batch which shows the amount packaged for each container size. Please be advised that the test batch must be completely packaged in the containers proposed for marketing.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call.

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,

Harvey A. Mearley for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Mikart

RTF
S. Middleton
4/22/99

March 17, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
Room 150
7500 Standish Place
Rockville, MD 20857-2773

Re: Abbreviated New Drug Application for Aminocaproic Acid Tablets USP 500 mg
Original Submission

Dear Mr. Sporn:

Enclosed please find two copies of an Abbreviated New Drug Application for Aminocaproic Acid Tablets USP 500 mg for your review and approval. Also included are three additional bound copies of all methodologies pertinent to this product.

Aminocaproic Acid Tablets USP 500 mg is manufactured by Mikart, Incorporated of Atlanta, Georgia, in accordance with current good manufacturing practices.

Should you have any questions, please do not hesitate to call or write. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/sl

Enclosures: duplicate bound ANDA
triplicate methodologies
5 volumes

RECEIVED
MAR 2 2 1999
GENERIC DRUGS

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432