CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74759

APPROVAL LETTER

ANDA 74-759

SEP 2 1998

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 September 25, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Aminocaproic Acid Syrup USP, 1.25 g/5 mL.

Reference is also made to your amendments dated April 9 and May 19, 1998.

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 Syrup, 1.25 g/5 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Amicar® Syrup, 1.25 g/5 mL of Immunex Corp.).

Under 21 CFR 314.70, 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 which 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,

/S/ 9/2/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74759

DRAFT FINAL PRINTED LABELING

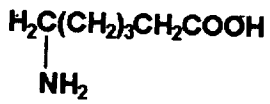
AMINOCAPROIC ACID SYRUP USP 25%

Code 658A00
Rev. 05/98

2

DESCRIPTION:

Aminocaproic acid USP is 6-aminohexanoic acid, which acts as an inhibitor of fibrinolysis. Its structural formula is:



$C_6H_{13}NO_2$ M.W. 131.18

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

Each 5 mL, for oral administration contains 1.25 g of aminocaproic acid and the following inactive ingredients: citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution and natural and artificial flavor.

The pH range of Aminocaproic Acid Syrup USP is between 6.1 and 6.6.

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. 65% 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 syrup is 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, 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 degree, plasmin activity. The drug should NOT be administered without a definite diagnosis and/or laboratory finding indicative of hyperfibrinolysis (hyperplasminemia).*

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.

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.

Laboratory Tests:

The use of aminocaproic acid should be accompanied by tests designed to determine the amount of fibrinolysis present. There are presently available (a) general tests such as those for the determination of the lysis of a clot of blood or plasma and (b) more specific tests for the study of various phases of the fibrinolytic mechanisms. These latter tests include both semiquantitative and quantitative techniques for the determination of profibrinolysin, fibrinolysin, and antifibrinolysin.

Drug Laboratory Test Interactions:
Prolongation of the template bleeding time has been reported during continuous intravenous infusion of aminocaproic acid at dosages exceeding 24 g/day. Platelet function studies in these patients have not demonstrated any significant platelet dysfunction. However, *in vitro* studies have shown that at high concentrations (7.4 mMol/L or 0.97 mg/mL and greater) EACA inhibits ADP and collagen-induced platelet aggregation, the release of ATP and serotonin, and the binding of fibrinogen to the platelets in a concentration-response manner. Following a 10 g bolus of aminocaproic acid injection, transient peak plasma concentrations of 4.6 mMol/L or 0.60 mg/mL have been obtained. The concentration of aminocaproic acid necessary to maintain inhibition of fibrinolysis is 0.99 mMol/L or 0.13 mg/mL. Administration of a 5 g bolus followed by 1 to 1.25 g/hr. should achieve and sustain plasma levels of 0.13 mg/mL. Thus, concentrations which have been obtained *in vivo* clinically in patients with normal renal function are considerably lower than the *in vitro* concentrations found to induce abnormalities in platelet function tests. However, higher plasma concentrations of aminocaproic acid may occur in patients with severe renal failure.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term studies in animals to evaluate the carcinogenic potential of aminocaproic acid and studies to evaluate its mutagenic potential have not been conducted. Dietary administration of an equivalent of the maximum human therapeutic dose of aminocaproic acid to rats of both sexes impaired fertility as evidenced by decreased implantations, litter sizes and number of pups born.

Pregnancy:
Teratogenic Effects. Pregnancy Category C. Animal teratological studies have not been conducted with aminocaproic acid. It is also not known whether aminocaproic acid can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Aminocaproic acid should be given to a pregnant woman only if clearly needed.

Nursing Mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when aminocaproic acid is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
Aminocaproic acid is generally well tolerated. The following adverse experiences have been reported:
General: Edema, headache, malaise.
Hypersensitivity Reactions: Allergic and anaphylactoid reactions, anaphylaxis.
Local Reactions: Injection site reactions, pain and necrosis.
Cardiovascular: Bradycardia, hypotension, peripheral ischemia, thrombosis.
Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting.
Hematologic: Agranulocytosis, coagulation disorder, leukopenia, thrombocytopenia.
Musculoskeletal: CPK increased, muscle weakness, myalgia, myopathy (see **WARNINGS**), myositis, rhabdomyolysis.
Neurologic: Confusion, convulsions, delirium, dizziness, hallucinations, intracranial hypertension, stroke, syncope.
Respiratory: Dyspnea, nasal congestion, pulmonary embolism.
Skin: Pruritus, rash.
Special Senses: Tinnitus, vision decreased, watery eyes.
Urogenital: BUN increased, renal failure. There have been some reports of dry ejaculation during the period of aminocaproic acid treatent. These have been reported to date only in hemophilia patients who received the drug after undergoing dental surgical procedures. However, this symptom resolved in all patients within 24 to 48 hours of completion of therapy.

OVERDOSAGE:

A few cases of acute overdosage with aminocaproic acid administered intravenously have been reported. The effects ranged from no reaction to transient hypotension to severe acute renal failure leading to death. One patient with a history of brain tumor and seizures experienced seizures after receiving an 8 gram bolus injection of aminocaproic acid. The single dose of aminocaproic acid causing symptoms of overdosage or considered to be life-threatening is unknown. Patients have tolerated doses as high as 100 grams while acute renal failure has been reported following a dose of 12 grams.

The intravenous and oral LD_{50} of aminocaproic acid were 3 and 12 g/kg respectively in the mouse and 3.2 and 16.4 g/kg respectively in the rat. An intravenous infusion dose of 2.3 g/kg was lethal in the dog. On intravenous administration, tonic-clonic convulsions were observed in dogs and mice.

No treatment for overdosage is known, although evidence exists that aminocaproic acid is removed by hemodialysis and may be removed by peritoneal dialysis. Pharmacokinetic studies have shown that total body clearance of aminocaproic acid is markedly decreased in patients with severe renal failure.

DOSAGE AND ADMINISTRATION:

For the treatment of acute bleeding syndromes due to elevated fibrolytic activity, it is suggested that 4 teaspoonfuls (5 g) of aminocaproic acid syrup be administered during the first hour of treatment, followed by a continuing rate of 1 teaspoonful (1.25 g) of syrup per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

HOW SUPPLIED:

Aminocaproic Acid Syrup USP, which contains aminocaproic acid 1.25 g/5 mL, is supplied as a clear, raspberry flavored syrup in bottles of 4 fl oz (118 mL), NDC 61748-044-34 and bottles of 16 fl oz (473 mL), NDC 61748-044-16.

Store at controlled room temperature, 15° to 30°C (59° to 86°F). **DO NOT FREEZE.**

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

Rx only

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Marketed by:
VersaPharm Incorporated
Marietta, GA 30065-1509

REFERENCES

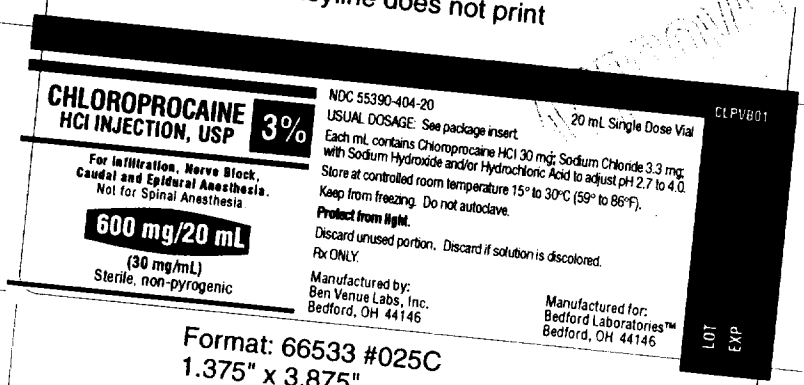
* Stefanini M, Dameshek W: The Hemorrhagic Disorders, Ed. 2, New York, Grune and Stratton, 1962; pp. 510-514.

Code 658A00

Rev. 06/98 –

SEP 9

Keyline does not print



Format: 66533 #025C
1.375" x 3.875"
PMS Black, PMS Pantone Green C

BEN VENUE
#C011294GA
PRINT SIDE

Store at controlled room temperature 15° to 30°C (59° to 86°F). Keep from freezing.

Protect from light.

Single dose container. Discard unused portion.

Discard if solution is discolored.

Do not autoclave.

Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

NDC 55390-404-20
20 mL Single Dose Vial

CHLOROPROCAINE 3%
HCl INJECTION, USP

For Infiltration, Nerve Block, Caudal and Epidural Anesthesia.
Not for Spinal Anesthesia.

600 mg/20 mL

(30 mg/mL)

Sterile, non-pyrogenic

BEDFORD LABORATORIES™

CLPCB01

55390-404-20

LOT

EXP

USUAL DOSAGE: See package insert.

Each mL contains Chloroprocaine HCl 30 mg; Sodium Chloride 3.3 mg; with Sodium Hydroxide and/or Hydrochloric Acid to adjust pH 2.7 to 4.0.

Rx ONLY.

NDC 55390-404-20
20 mL Single Dose Vial

CHLOROPROCAINE 3%
HCl INJECTION, USP

For Infiltration, Nerve Block, Caudal and Epidural Anesthesia.
Not for Spinal Anesthesia.

600 mg/20 mL

(30 mg/mL)

Sterile, non-pyrogenic

BEDFORD LABORATORIES™

Format Number: 66790 #009B
Pantone Green
Black

Prepared by
Mark Zarnstorff
Checked by

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74759

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. # 3

2. ANDA # 74-759

3. NAME AND ADDRESS OF APPLICANT

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

4. LEGAL BASIS FOR SUBMISSION
Reference drug: Amicar Syrup (Lederle - Immunex). The applicant states that as per Section 505 (j)(2)(vii) of the Food, Drug and Cosmetic Act, to the best of their knowledge the reference drug is not covered by any patent or marketing exclusivity. This drug product was reviewed under DESI ACT and determined to be acceptable for an ANDA.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None.

7. NONPROPRIETARY NAME
Aminocaproic Acid Syrup, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 9/25/95
ANDA Original amendment: 11/17/95
Amendment: 4/25/96
ANDA Amendment: 12/15/97
Amendment: 4/9/98
Amendment: 5/19/98

FDA:
Refusal to file: 11/7/95
Date of filing: 11/27/95
Biowaiver granted: 3/28/96
Chemistry and Labeling deficiency letter: 4/12/96
Chemistry deficiency by fax: 3/10/98

10. PHARMACOLOGICAL CATEGORY
Enhancing hemostasis

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA:
DMF:

13. DOSAGE FORM
Syrup

14. POTENCY
1.25 g/5 mL

15. CHEMICAL NAME AND STRUCTURE
Aminocaproic Acid

16. RECORDS AND REPORTS
N/A

17. COMMENTS
No outstanding Chemistry deficiencies found.

18. CONCLUSIONS AND RECOMMENDATION
ANDA recommended for approval.

19. REVIEWER: DATE COMPLETED:

Radhika Rajagopalan, Ph.D. 5/4/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74759

BIOEQUIVALENCY REVIEW(S)

MAR 26 1996

Aminocaproic Acid, USP
1.25 g/ 5 ml, Syrup
ANDA # 74-759
Reviewer: A.P.Patel
x:\apatel\74759W.s95

Mikart, Inc
Atlanta, Georgia
Submission Date:
Sept. 25, 1995
Nov.17, 1995

Review of a Waiver Request

Introduction:

Aminocaproic acid is useful in enhancing hemostasis when fibrinolysis contributes to bleeding.

Objective:

The firm has requested that the *in-vivo* Bioequivalence requirements for the test product be waived under the provisions of CFR 320.22(b)(3). The reference product is Amicar Syrup, 1.25 g/5ml, manufactured by Lederle Laboratories.

Comments:

1. The test product is an oral syrup containing the same active ingredient (6-aminocaproic acid) in the same concentration (1.25 g/ 5 ml) as the reference product.

2. The Firm was granted a waiver from in vivo Bioequivalency studies for this product (ANDA # 74-144). The proposed formulation is qualitatively and quantitatively similar to previously approved formulation except the proposed formulation does not contain sodium benzoate and potassium sorbate.

3. The test product contains no inactive ingredient known to significantly affect absorption of the active ingredient. The ingredients of the test and reference drugs are shown in Table 1.

4. The test product does not contain preservative. Division of Chemistry should address stability and microbial contamination issues.

Dificiencies: None

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Mikart, Inc. demonstrates [illegible] 320.22(b)(3). [illegible] bioequivalence study for aminocaproic acid, USP 1.25 g/5 ml syrup is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test syrup to be bioequivalent to Amicar Syrup, 1.25g / 5 ml manufactured by Lederle.

The firm should be advised of the recommendation.

/S/ 3/25/96

A.P.Patel
Division of Bioequivalence
Review Branch III

RD Initialed R.M. Mhatre
FT Initialed R.M. Mhatre /S/ Date: 3/26/96

Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

ANDA# 74-786, HFD-600 (Hare), HFD-630, HFD-658 (R.M.Mhatre, A.P.Patel), Drug File, Division File.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74759

CORRESPONDENCE

ANDA 74-759

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

JAN 11 1996

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 November 7, 1995, and your amendment dated November 17, 1995.

NAME OF DRUG: Aminocaproic Acid Syrup USP. 1.25 g/5 mL

DATE OF APPLICATION: September 25, 1995

DATE OF RECEIPT: October 2, 1995

DATE ACCEPTABLE FOR FILING: November 27, 1995

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

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

Should you have questions concerning this application contact:

Kassandra Sherrod
Consumer Safety Officer
(301) 594-1300

Sincerely yours,

/S/ 1/11/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-759
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-[illegible]/Reading File
HFD-[illegible]/Mannetti

Endorsements: HFD-615/PRickman, Actg Chief
HFD-615/SMiddleton, CST
HFD-625/BArnwine
WP File x:\wpfile\middleton\74-759.ack
F/T by bcw/11-30-95
ANDA Acknowledgement Letter!
RTF 11/7/95
ACK 11/17/95

ANDA 74-759

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

APR 12 1996

Dear Ms. McDonald:

This is in reference to your abbreviated new drug application dated September 25, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Aminocaproic Acid Syrup USP, 1.25 g/5 mL.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Please clarify the following discrepancy: The composition statement on page 88 states that methylparaben NF is used at % and propylparaben NF is used at % levels. However, the demonstration batch (page 698) has a formula per 5 mL level that is double the amount on page 88. Methylparaben NF is used at % and propylparaben NF is used at % level. In addition, the batch demonstrated on page 888 (exhibit batch made at % parabens concentration) the levels of parabens agree with the composition statement on page 88. Is the composition statement on page 88 incorrect? If so, modify the statement and provide an adequate explanation. Also note that all of these formulations are identified with the same MF

2. We notice the COA is provided by the for Aminocaproic Acid USP, as well as, by the Please clarify the connection between and

3. For sodium saccharin USP, correspondence and COA are included in the application. However, please note that the COA on page 231 does not bear a lot or batch number and date. The letters from are dating back to September and October of 1985. Please provide us a copy of a recent COA with batch number. Also we notice that the manufacturer is identified as on pages 419 and 400. Please clarify the connection between and

4. Please identify if purified water USP is generated in-house.

5. Please provide us information regarding the reference standard material used for assaying the drug substance. Also, include as Certificate of Analysis for any in-house reference standard used for assays.

6. We notice that the mixing times are not identified for each step after an ingredient is added, with the exception of the step. The demonstration batch and the master batch record simply state to dissolve addition' or 'until dissolved'. How do you ensure complete dissolution of ingredients? Please include mixing times and speed.

7. The contents of the auxiliary tank are poured into the main vessel, . Is there any loss of parabens due to this step? How do you ensure complete transfer?

8. The manufacturing instructions call for storing the drug product in drums (~100 L size). What are some typical holding times (until homogeneity testing is done)? Holding times need to be established and validated based on microbiology data prior to implementation.

9. Please explain the operations described in pages 725-728.

10. Please modify your reprocessing statement with the following changes:

2. Please modify the last sentence to include an approved supplemental application by the Food and Drug Administration prior to implementation of any rework procedure.

11. Please note that the enclosed Letter of Authorization from is dated 12/6/89 (6 yrs. old). Please provide us a recent LOA from

12. We note your protocol for substitution of packaging components (page 1015). Please be aware that a change from to and/or a change in container size (except solid oral dosage form) without a change in the container and closure system will need an approved supplement prior to implementation as per 21 CFR 314.70(2)(vii and/or viii). The stability data submitted in this application are only for supporting marketing in glass bottles (4 and 16 fl oz. sizes). Please acknowledge this comment and revise your protocol.

13. Please include data regarding the stability of standard and sample preparations. Are the standard/sample preparations kept and used for a period of >24 hrs.? If so, stability of those solutions needs to be generated again.

14. The degradation study samples of aminocaproic a need to be analyzed using and reported in the validation package.

when samples are degraded. Hence, please provide these data.

15. The validation for the drug product needs to address the following topics:

1. Method ruggedness: column to column performance, analyst-to-analyst performance and day-to-day reproducibility.
2. Method robustness: this new element for method validation is a compendial requirement (USP XXIII).

16. The stability tables have no information regarding unknown degradation products of aminocaproic acid. Please provide these data in future amendments to this application.

17. We notice in your stability protocol you have not included a commitment as to how the samples will be stored. The actual data indicate that the bottles are stored horizontally. Please modify the demonstration and commercial stability protocols to store samples in the upright and horizontal configurations.

18. Please provide ambient temperature stability data for these container configurations during future correspondence regarding this application.

19. We notice a substantial time delay between the test date and sampling date. In fact the 60 day stability samples had not been analyzed for 90 days and the 90 day samples had not been analyzed for 60 days after they were pulled from the stability chamber. We need to know the conditions these samples were stored in for the time period they were not analyzed. We also need a rationale for this type of delay in analysis and a commitment from you for completing analysis within 30 days from the date they were pulled.

20. The commercial stability protocol needs to be revised to include the antimicrobial effectiveness test for the initial three batches at initial and expiry test stations, even though the parabens are assayed chemically.

21. Please note that if container material is changed from glass to HDPE material an approved supplement will be required with at least 3 months of accelerated stability data prior to implementation.

B. Labeling Deficiencies

1. CONTAINER (4 fl oz, 16 fl oz)

Revise the temperature storage recommendations to read as follows:

2. INSERT

a. DESCRIPTION

i. Increase the print size of the structural formula.

ii. To be in accord with USP 23, revise the molecular weight to read "131.18" rather than

iii. Revise the last paragraph to read as follows:

Each 5 mL, for oral administration contains:

iv. We encourage the inclusion of pH ra... of the syrup.

b. INDICATIONS AND USAGE

i. Revise the first sentence of paragraph one to read:

Aminocaproic acid syrup is...

ii. Delete the hyphen from "nonsurgical" in the last paragraph.

c. PRECAUTIONS

Drug Laboratory Test Interactions - ...bolus of aminocaproic acid injection, transient...

d. OVERDOSAGE

Paragraph 2 — Delete

e. HOW SUPPLIED

i. See comment under CONTAINER.

ii. Revise to read:

supplied...

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling. Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application you may request an opportunity for a hearing.

Sincerely yours,

/S/ 4/11/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-759

MAR 28 1996

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

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section [illegible] of the Federal Food, Drug and Cosmetic Act for Aminocaproic Acid Syrup USP, 1.25g/5 [illegible]

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-759

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

NOV 7 1995

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated September 25, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Aminocaproic Acid Syrup USP, 1.25 g/5 mL.

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 reasons:

> You have failed to provide evidence demonstrating the bioequivalence of your proposed drug product with the reference listed drug. Please either provide a bioequivalence study or a request for a waiver of in-vivo bioequivalence requirements per 21 CFR 320.22(a)(3).

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

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(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 11/7/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

Return to file
10/11/95
10/12/95

September 25, 1995

labeling review completed
2/25/96

Mr. Charles Ganley, Acting 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 Syrup USP 1.25 g per 5 mL.
Original Submission

Dear Mr. Ganley:

Enclosed please find two copies of an Abbreviated New Drug Application for Aminocaproic Acid Syrup USP 1.25 g per 5 mL for your review and approval. Also included are three additional bound copies of all methodologies pertinent to this product.

Aminocaproic Acid Syrup USP 1.25 g per 5 mL 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/sw

Enclosures: duplicate bound ANDA's
triplicate methodologies

RECEIVED
OCT 02 1995
GENERIC DRUGS

1750 CHATTAHOOCHEE AVENUE, N.W., ATLANTA, GEORGIA 30318-2112 PHONE: 404-351-4510 FAX: 404-350-043

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

505(j)(2)(A)(ii)
11/30/95
Original

AC

November 17, 1995

Dr. Charles Ganley, Acting 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 74-759 Aminocaproic Acid Syrup USP 1.25 g per 5 mL
AMENDMENT TO AN UNAPPROVED APPLICATION

Dear Dr. Ganley:

Mikart has received your letter dated November 7, 1995 regarding the above application. We would like to respond by submitting the attached request for a waiver of in-vivo bioequivalence under 21 CFR 320.22 (b) (3).

Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/sw

Enc.

750 CHATTAHOOCHEE AVENUE, N.W., ATLANTA, GEORGIA 30318-2112 PHONE: 404-351-4510 FAX: 404-350-0432

Mikart

May 19, 1998

DRUG AMENDMENT
N/AF

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 74-759 Aminocaproic Acid Syrup USP 1.25 g per 5 mL
MINOR AMENDMENT TO AN UNAPPROVED APPLICATION

Dear Mr. Sporn:

Mikart has received your facsimile dated May 15, 1998 regarding the above application. We have revised the container labels and inserts as suggested. Attached, are side by side comparisons of the proposed labeling with previously submitted labeling. Also, please find 12 copies of final printed labeling enclosed. Three copies have been mounted and nine additional copies have been included separately for your review.

With the submission of this information, there are no longer any outstanding deficiencies, and we respectfully request that the application be approved. 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
Executive Vice-President

CBM/lac

RECEIVED
MAY 21 1998
GENERIC DRUGS

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

Mikart

notified PS 4/22/98

April 9, 1998

ORIG AMENDMENT

N/Am

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 74-759 Aminocaproic Acid Syrup USP 1.25 g per 5 mL
MINOR AMENDMENT TO AN UNAPPROVED APPLICATION

Dear Mr. Sporn:

Mikart has received your letter dated March 10, 1998 regarding the above application. We would like to respond now to the issues raised. We have used the outline of your letter to organize our response.

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
Executive Vice-President

CBM/lac

RECEIVED
APR 10 1998
GENERIC DRUGS

Received 4-21-98

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

Mikart

December 15, 1997

FPL
NDA CRIS AMENDMENT
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 74-759 Aminocaproic Acid Syrup USP 1.25 g per 5 mL
MAJOR AMENDMENT TO AN UNAPPROVED APPLICATION

Dear Mr. Sporn:

Mikart has received your letter dated April 12, 1996 regarding the above application. We would like to respond now to the issues raised. We have used the outline of your letter to organize our response.

Mikart would also, with this submission, like to add as a designated testing facility for organic volatile impurities testing (all methods) in raw materials. Mikart will be submitting a blanket supplement for all other approved applications to provide for this addition. All raw material specification sheets, for which organic volatile impurities testing is required, will be revised upon the approval of the blanket supplement, and submitted in subsequent annual reports. Information from and a revised list of designated facilities are included with this amendment.

Mikart has become aware that the reference product for this application is not currently available in the marketplace due to a recent recall. Information obtained from public sources indicates that it may take several months for that product to return to distribution. Since Aminocaproic Acid Syrup may be used in serious or life-threatening circumstances, we ask that the office view this amendment as a submission under 21 CFR 314.500.

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
Executive Vice-President

CBM/ds

RECEIVED
DEC 23 1997
GENERIC DRUGS

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

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

April 25, 1996

NDA ORIG AMENDMENT
N/A A

RECEIVED
MAY 07 1996
GENERIC DRUGS

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 74-759 Aminocaproic Acid Syrup USP 1.25 g per 5 mL
AMENDMENT TO AN UNAPPROVED APPLICATION

Dear Mr. Sporn:

It has come to our attention that the plant address for , designated supplier of the active ingredient, provided in the original application, is incorrect. We would like to amend the above application to include corrected information. A revised listing of the designated supplier of the drug substance and revised master manufacturing formula for the production batch size are attached.

Thank you for your cooperation in the review of this material. Please feel free to contact us should you have any questions or concerns.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/sw

Enclosures

1750 CHATTAHOOCHEE AVENUE, N.W., ATLANTA, GEORGIA 30318-2112 PHONE: 404-351-4510 FAX: 404-350-043