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