CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-287/S-002

Name: Fragmin (Dalteparin Sodium) Injection

Sponsor: Pharmacia Inc.

Approval Date: March 18, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-002

APPROVAL LETTER

15.1

NDA 20-287/S-002

MAR 18 1996

Pharmacia Inc.
Attention: Susan M. Mondabaugh, Ph.D.
P.O. Box 16529
Columbus, Ohio 43216-6529

Dear Dr. Mondabaugh:

Please refer to your July 7, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium injection).

The supplemental application provides for a 5000 IU dosage form.

We have completed the review of this supplemental application and it is approved.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Karen Oliver
Regulatory Health Project Manager
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-287/S-002
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/S.Fredd
HFD-180/J.Gibbs
HFD-180/J.Sieczkowski
HFD-820/Yuan Yuan Chiu (only for chemistry supplements)
HFD-80
DISTRICT OFFICE
HFD-232
HFD-205 Freedom of Information

drafted: KO/March 13, 1996
r/d Initials: J.Siezckowski 03/14/96
r/d Initials: J.Gibbs 03/14/96
r/d Initials: S.Fredd 03/15/96 K. Oliver 03/18/96
final: KO/03/18/96/c:\wpwin\karenfil\nda\20287603.0ko

APPROVAL 3/18/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-002

APPROVABLE LETTER

15.1

JAN - 4 1996

NDA 20-287/S-002

Pharmacia Inc.
Attention: Susan M. Mondabaugh, Ph.D.
P.O. Box 16529
Columbus, Ohio 43216-6529

Dear Dr. Mondabaugh:

Please refer to your July 7, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium injection).

The supplemental application provides for a 5000 IU dosage form.

We have completed the review of this supplemental application and it is approvable. Before this supplement may be approved, however, it will be necessary for you to obtain approval of supplement 003 for NDA 20-287 to provide labeling for the use of the 5000 IU dosage form.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

The 5000 IU dosage form may not be marketed until you have been notified in writing that this supplemental application is approved.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Should you have any questions, please contact:

Karen Oliver
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-287/S-002
HFD-180/Div. Files
HFD-80
HFD-180/CSO/K.Oliver
HFD-180/J.Gibbs
HFD-180/J.Sieczkowski
DISTRICT OFFICE
r/d Initials: J.Sieczkowski 01/02/96
r/d Initials: J.Gibbs 01/02/96
r/d Initials: S.Fredd 01/03/96

drafted: KO/January 2, 1996 KOliver 01/03/96
Final: KO/01/03/96/c:\wpwin\karenfil\nda\20287601.0ko

APPROVABLE (AE) SF 1/3/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-002

CHEMISTRY REVIEW

005 15-1

CHEMIST REVIEW: #1	1. Organization: HFD-180	2 NDA Number: 20-287	
Name and Address of Applicant (City & State): armacia Incorporated ,001 Post Road Dublin, Ohio 43017 DEC - 7 1995		4. AF Number: 5. Supplement(s)	
		Number(s):	Dates(s):
6. Name of Drug: FRAGMIN™ Injection	7. Nonproprietary Name: dalteparin sodium	SCF-002	7 JUL 1995
8. Supplement Provides for: a new Fragmin (dalteparin sodium) Injection formulation with a potency of 5000 IU (anti-Factor Xa)/0.2. mL.		9. Amendments and Other (Reports, etc.) Dates: NDA Chem. Rev. #1 12 MAY 1993 NDA Chem. Rev. #2, 4 FEB 1994 NDA Chem. Rev. #3, 2 AUG 1994	
10. Pharmacological Category: Anticoagulant	11. How Dispensed: RX XXX OTC ___	12. Related ND/NDA/DMF(s): 1. SE 2-003/7JUL 1995 2. See NDA 20-287. Chem. Rev. #3, 2 AUG 1994 for final DMFReviews and status.	
13. Dosage Form: Injection	14. Potency: 2500 IU (anti-Factor Xa) 5000 IU (anti-Factor Xa) per 0.2 mL syringe.		
15. Chemical Name and Structure: See NDA 20-287, Chem. Rev. #1.		16. Records and Reports: Current _____ Yes _____ No Reviewed _____ Yes _____ No	

17. Comments:
See Review Notes

cc: NDA 20-287
HFD-180/Div/File
HFD-181/CSO/KOliver
HFD-180/SFredd
HFD-180/JSieczkowski
R/D init by: JGibbs/12-1-95
dob DRAFT 12-4-95\F/T **12-7-95**\Wp: c:\wpfiles\chem\S\20287.002.1JS

18. Conclusions and Recommendations: Based on the submitted supplemental information and the information cross referenced to in the Original NDA 20-287, this supplement is recommended for approval. Pharmacia Inc. should be notified of the approval by letter and in the letter of approval they should be advised that we expect their cooperation in methods validation of the tests and assay methods for Fragmin Injection, 5000 IU (anti-Factor Xa). The approval letter should be drafted by the CSO for the Division Director's signature.
NOTE: See the recommendation for methods validation under E. Methods Validation.

19. Reviewer 12/7/95

Name:	Signature:	Date Completed:
Joseph Sieczkowski, Ph.D.	Joseph Sieczkowski 12-7-95	November 29, 1995

REVIEW NOTES

Preface:
The review format used is the one for the review of an Original NDA. Most of the information submitted for this supplement is by cross reference to the Original NDA submission for Fragmin (dalteparin sodium) Injection, 2500 IU and 5000 IU/0.2 mL single dose syringe. The following chemistry reviews were performed for the Original NDA:

Chemistry Review #1 (May 12, 1993)

SUBMISSION TYPE		DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	[RS]	22 DEC 1992	30 DEC 1992	14 JAN 1993
Amendment	[BZ]	12 JAN 1993	21 JAN 1993	26 JAN 1993
Amendment	[BZ]	12 MAR 1993	16 MAR 1993	18 MAR 1993
Amendment	[BS]	12 MAR 1993	16 MAR 1993	18 MAR 1993

Chemistry Review #2 (February 4, 1994)

SUBMISSION TYPE		DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	[AC]	8 NOV 1993	10 NOV 1993	16 NOV 1993

Chemistry Review #3 (August 2, 1994)

SUBMISSION TYPE		DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	[BC]	24 JUN 1994	27 JUN 1994	30 JUN 1994
Amendment	[BM]	17 MAY 1994	18 JUN 1994	12 JUL 1994

A. Drug Substance:
(Review Items 1. through 8.)

Information Submitted (page 001).
a. Cross reference to drug substance information in:
1. Original NDA dated August 6, 1992.
2. NDA Amendments dated November 8, 1993 and June 24, 1994.

NDA Approval dated December 22, 1994.

COMMENT:
The drug substance to be used is that which was provided and approved in the Original NDA 20-287. The CMC and specifications section for dalteparin sodium is adequate by reference to the Original NDA 20-287 and its amendments. No additional information will be requested.

Redacted 14 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

NOTE: The package insert is the subject of Supplement SE2-003 which is for a new indication using the 5000 IU (anti-Factor Xa) drug product potency.

COMMENT:
The labeling for the single dose syringe, the blister package for the single dose syringe and the box label for the blister package (drug product labeling) appear to be appropriate and adequate. The product labeling for the 5000 IU (anti-Factor Xa) potency is the same as the 2500 IU (anti-Factor Xa) product labeling except that it now exhibits the new 5000 IU potency.

G. ESTABLISHMENT INSPECTION.

Electronic Mail Message

Date: 28-Nov-1995 02:20pm EST
From: Joseph David Doleski
DOLESKI
Dept: HFD-324 MPN1 265
Tel No: 301-827-0062 FAX 301-827-0145

TO: Karen Oliver (OLIVERK)

CC: John Gibbs (GIBBS)
CC: Joseph Sieczkowski (SIECZKOWSKI)

Subject: FWD: Fragmin 20-287/S-002

Karen,

This is just to confirm that an EER is not needed for a supplement for a new strength. In this case going from 2,500 IU to 5,000 IU. In general we do not need EERs for a chenge in formulation because it (generally) doesn't significantly impact the manufacturing process. You may proceed with an action for this supplement.

Dave

COMMENT:
It is expected that the increase in potency for Fragmin Injection from 2500 IU to 5000 IU will not impact the manufacturing process. Therefore an EER will not be requested for this supplement.

H. DRAFT DEFICIENCY LETTER.
None.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Date July 7, 1995

15.1

Pharmacia

Reference NDA 20-287

SLK002

AIRBORNE

Stephen B. Fredd, M.D., Director
Food and Drug Administration
Division of Gastrointestinal and Coagulation Drug Products
HFD-180
Central Document Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 20-287 REF. NO. 002

NDA SUPPL FOR SLR SCE

RE: NDA 20-287
FRAGMIN™ (dalteparin sodium injection)

CMC Section
Draft Labeling
Supplement: S002

ORIGINAL

Dear Dr. Fredd:

Reference is made to approved NDA 20-287 for Fragmin™. Reference is made to the March 1, 1995 telephone conversation between Bronwyn Collier of your Division and Michael Trapani and myself of Pharmacia during which we agreed that the Bergqvist 3 study report would be submitted as an integral part of an efficacy supplement supported by a separate CMC supplement for the 5000 IU dosage form that would cross-reference NDA 20-287.

We are herewith submitting the CMC supplemental information that supports the supplement of clinical data from the Bergqvist 3 study. This supplement provides no changes to the chemistry, manufacturing and controls data already provided in approved NDA 20-287. Data from the original NDA are incorporated into this supplement by cross-reference. The draft labeling has been revised to include the proposed enlargement of the indication for use of Fragmin.

If your have any comments or questions about this submission, please contact me by telephone at 614/764-8184 or by FAX at 614/764-8125.

Sincerely,

Ann Hards, Ph.D.

Ann Hards, Ph.D.
Manager, Regulatory Affairs

7/25/95

Postal address
Pharmacia Inc.
Post Office Box 16529
Columbus, Ohio 43216-6529
USA

Visiting address
7001 Post Road
Dublin, Ohio 43017
USA

Telephone
614-764-8100

Telex
246-620

Telefax
614-761-8102

15.1

NDA 20-287/S-002

Pharmacia Inc.
Attention: Ann Hards, Ph.D.
Post Office Box 16529
Columbus, OH 43216-6529

JUL 26 1995

Dear Dr. Hards:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Fragmin (dalteparin sodium injection)

NDA Number: NDA 20-287

Supplement Number: S-002

Therapeutic Classification: Standard

Date of Supplement: July 7, 1995

Date of Receipt: July 11, 1995

This supplement provides for a 5000 IU dosage form.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 9, 1995 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Karen Oliver
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-287/S-002
HFD-180/Div. Files
HFD-80
HFD-180/CSO/K.Oliver

drafted: KO/July 24, 1995 K. Oliver 07/24/95
Final: KO/07/24/95/c:\wpwin\karenfil\nda\20287507.0ko

SUPPLEMENT ACKNOWLEDGEMENT