CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-026

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.

Approval Date: September 14, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-026

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-026

APPROVAL LETTER

NDA 20-164/S-026

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Dennis Jurgens
500 Arcola Road
P.O. box 1200
Collegeville, PA 19426-0107

Dear Mr. Jurgens:

Please refer to your supplemental new drug application dated March 24, 1999, received March 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submission dated August 26, 1999.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for: qualifying an increased batch size ——— of Lovenox® 30 mg/0.3 mL and 40 mg/0.4 mL pre-filled syringes manufactured at the Rhone-Poulenc Rorer, 180, rue Jean Jaures, Maisons-Alfort, France site. Your submission stated thirty days from the date of your March 24, 1999 letter as the implementation date for the change.

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

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

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Liang Zhou, Ph.D.
Acting Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-164/S-026
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/Reviewers and Team Leaders
HFD-095/DDMS-IMT
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/September 14, 1999
final: KO/09/14//99/c:\data\mydocuments\NDA20164-S-026-09-14-99-AP.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-026

CHEMISTRY REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls Supplement

NDA 20-164 SUPPLEMENT: SCS-026 CHEM REVIEW: #1 REVIEW DATE: 8/31/99

SUBMISSION TYPE	DATES DOCUMENT	CDER
ORIGINAL	24 MAR 1999	26 MAR 1999
AMENDMENT BC	26 AUG 199	30 AUG 1999

SUPPLEMENT PROVIDES FOR: an increase in drug product manufacture to a ——— drug product batch size using a ——————————— ——— on Line — at the Maisons-Alfort site for the production of 0.3 and 0.4 mL syringes with manufacturing

[ ]

NAME & ADDRESS OF APPLICANT:
Rhone-Poulenc Rorer
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

DRUG PRODUCT NAME:

Proprietary:	Lovenox® Injection
Nonproprietary/USAN:	enoxaparin sodium injection
Code Name/#:	RP4563
Chem.Type/Ther.Class:	low molecular weight heparin

PHARMACOLOGICAL CATEGORY: --

INDICATION:
For the treatment of deep vein thrombosis or pulmonary embolism.

DOSAGE FORM: Sterile Solution/small volume parenteral
STRENGTH: 30,40,60,80,100 mg per prefilled syringe/100 mg per mL.
ROUTE OF ADMINISTRATION: Subcutaneous injection

HOW DISPENSED: XX Rx ___OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See NDA Chemistry Review #1.

SUPPORTING DOCUMENTS: NONE

RELATED DOCUMENTS (if applicable):
SCS-027/April 8, 1999.

CONSULTS:
Microbiology: See review by Patricia F. Hughes, Ph.D., Chemistry Review item, 8. Microbiology.

REMARKS/COMMENTS:
1. SS-CBE Supplement.
2. EER - Acceptable, August 17, 1999.

CONCLUSIONS & RECOMMENDATIONS:
Based on the submitted chemistry, manufacturing, and controls information and the microbiologist's recommendation assuring microbiological quality, it is recommended that the supplement be approved. The CSO should prepare the appropriate approval letter.

Joseph Sieczkowski, Ph.D.
Review Chemist, HFD-180

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-164/S-026
HFD-180/Div File/NDA 20-164
HFD-180/L.Talarico
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-181/CSO/K.Oliver
R/D Init by: E.Duffy/
dob DRAFT 8/25/99/F/T 9-1-99
Word : c:\wordfiles\chem\S\20164026.1JS

REVIEW NOTES

A. DRUG SUBSTANCE
Not Applicable (N/A)

B. DRUG PRODUCT
1. COMPONENTS: N/A
2. COMPOSITION: N/A
3. SPECIFICATIONS & METHODS FOR DRUG PRODUCT INGREDIENTS: N/A

4. MANUFACTURER:
Rhone-Poulenc Rorer
Pharmaspecialities
180, rue Jean Jaures
94700 Maisons-Alfort, FRANCE

2 METHODS OF MANUFACTURING AND PACKAGING
A. Production Operations
NOTE: The following is an excerpt of some of the information submitted in support of the proposed change.

a. Titles of sections submitted:
4.2.2.1 Manufacturing Summary Report Entitled "Enoxaparin Sodium Solution (100 mg/mL) Syringes 30 mg and 40 mg" Manufacturing Process S.A.I.3.
4.2.2.2 Sterilization Process Validation Report Entitled "Lovenox® 30 mg and 40 mg Syringe Sterilization Process Validation - [redacted] Manufacturing Process."

A batch record extract and executed batch records for 3 lots of 40mg/0.4mg syringes manufactured with this increased batch size are included in this submission.

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW

lets from the market are adequate in support of the proposed supplemental request.
ADEQUATE

C. INVESTIGATIONAL FORMULATIONS: N/A

D. ENVIRONMENTAL ASSESSMENT: (page 4-264)
An environmental assessment (EA) is not necessary for this type of supplemental request. However, RPR made a request for a categorical exclusion from EA requirements under 21 CFR 25.31(b). Enoxaparin Sodium is calculated to be 4.92×10^{-2} ppb or 49.2 ppt and is below the 1 ppb EIC. (bc Amendment August 26, 1999.)

E. METHODS VALIDATION: N/A

F. LABELING: N/A

G. ESTABLISHMENT INSPECTION: (August 17, 1999).
The EER notes "Acceptable" for the manufacturing facility at Maisons-Alfort, FRANCE, dated April 6, 1999. (Based on the January, 1999 Inspection for Supplement 019 and previous firm history.)

H. COMMENTS AND LIST OF DEFICIENCIES: None

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-026

MICROBIOLOGY REVIEW

REVIEW TO HFD-180
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY TEAM
MICROBIOLOGIST REVIEW OF AN SUPPLEMENT
11 MAY 1999

A. NDA 20-164/SCS-026

PRODUCT NAME: Lovenox Injection
Enoxaparin sodium

APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

DOSAGE FORM: Sterile Solution in strengths of 30, 40, 60, 80, and 100 mg for Subcutaneous injection

METHOD OF STERILIZATION: [redacted]

PHARMACOLOGICAL CATEGORY: For the treatment of deep vein thrombosis or pulmonary embolism

B. INITIAL APPLICATION DATE: 24 March 1999
ASSIGNED FOR REVIEW: 14 April 1999

C. REMARKS: The CBE Supplement 026, contains data and information submitted to support an increase in batch size for Lovenox 30 mg/0.3 mL and 40 mg/0.4 mL pre-filled syringes. These pre-filled syringes are manufactured at Rhone-Poulenc Rorer Pharmaspecialites, 180, rue Jean Jaures, 94700 Maisons-Alfort, France, CFN # FCFR218, the approved site for manufacturing. The applicant proposes to use Line – to manufacture syringes with a batch size of [redacted]. This change is being made to increase production capacity.

D. CONCLUSIONS: The CBE supplement S-026 to the NDA 20-164, which provides for Lovenox Injection, is recommended for approval from the standpoint of product quality microbiology. Please see section E for Review Notes.

Patricia F. Hughes, Ph. D.
Review Microbiologist

cc.: Original NDA 20-164
HFD-160 /Consult File
HFD-805/PFHughes
HFD-180/KOliver
HFD-180/Division File
Drafted by PFHughes/11 May 1999
R/D Initialed by PHCooney

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MICROBIOLOGY REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-026

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-164/S-026

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Dennis Jurgens
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Mr. Jurgens:

We acknowledge receipt of your manufacturing supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lovenox® (enoxaparin sodium) Injection

NDA Number: NDA 20-164

Supplement Number: S-026

Date of Supplement: March 24, 1999

Date of Receipt: March 26, 1999

This supplement proposes the following: qualifying an increased batch size ——— of Lovenox® 30 mg/0.3 mL and 40 mg/0.4 mL pre-filled syringes manufactured at the Rhone-Poulenc Rorer, 180, rue Jean Jaures, Maisons-Alfort, France site. Your submission stated thirty (30) days of the date of your letter as the implementation date for the change.

We note that you have submitted this supplement under 21 CFR 314.70(c), "Special Supplement - Changes Being Effected."

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 May 25, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 26, 1999.

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

Food and Drug Administration
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

If you have any questions, please contact me at (301) 827-7310.

Sincerely,

Karen Oliver, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-164/S-026
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski

DISTRICT OFFICE
Drafted by: KO/April 1, 1999
final: KO/04/01/99
filename: c:\mydocuments\20164-04-01-99-S-026-ackCBE

SUPPLEMENT ACKNOWLEDGEMENT (AC)