CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-024

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.

Approval Date: July 22, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-024

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-024

APPROVAL LETTER

NDA 20-164/S-024

JUL 22 1999

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 January 26, 1999, received January 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection

This supplemental new drug application provides for alternate methods for the enoxaparin sodium specifications "Residual solvents: ——————————" and "Aqueous solution: - clarity".

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.

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

Sincerely,

ERIC P. DUFFY 7/22/99

Eric P. Duffy, Ph.D.
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-024
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/July 7, 1999 K Oliver 07/07/99
final: KO/07/07/99/c:\mydocuments\NDA20164-S-024-07-07-99-AP

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-024

CHEMISTRY REVIEW

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

NDA 20-164 SUPPLEMENT SCS-024 CHEM. REVIEW:#1 REVIEW DATE: 7-7-1999

SUBMISSION TYPE	DATES DOCUMENT	CDER
ORIGINAL	26 JAN 1999	27 JAN 1999
AMENDMENT		

SUPPLEMENT PROVIDES FOR: a new regulatory analytical method which is a ———————————— method for residual solvents in enoxaparin sodium, and for an alternate clarity of a solution method which is a ———————— method for a enoxaparin sodium aqueous solution.

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/#:	RP54563
Chem.Type/Ther.Class:	low molecular weight heparin

PHARMACOLOGICAL CATEGORY: anti-thrombotic

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/syringe (100mg/mL)
ROUTE OF ADMINISTRATION: subcutaneous injection
HOW DISPENSED: XX Rx ___OTC

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

SUPPORTING DOCUMENTS: NONE

RELATED DOCUMENTS (if applicable): NDA 20-164/SCM-022 and SCS-023.

CONSULTS: NONE

REMARKS/COMMENTS:
1. Specifications for enoxaparin sodium remain the same.
2. Methods validation package for FDA Labs is not necessary.

CONCLUSIONS & RECOMMENDATIONS:
The submitted information is adequate in support of the supplement request for an additional regulatory method which is a ———— analytical method for drug substance residual solvents, and for an alternate method for clarity of an enoxaparin sodium aqueous solution. The CSO should prepare a supplemental approval letter for the Team Leader's signature.

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

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

cc:
NDA 20-164/SCS-024
HFD-180/Div File/NDA 20-164
HFD-180/L.Talarico
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-180/CSO/K.Oliver
R/D Init by: E.Duffy
dob Draft 7-22-99/F/T 7-22-99/WORD: N:\wordfiles\chem\S\20164024.1JS

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW

COMMENT:
The proposed ———————— analytical method, on the basis of the submitted information, appears to be a slight improvement over the approved ———————— analytical method. The proposed ———— analytical method appears adequate and may be adopted as a regulatory method for the analysis of residual solvents in the drug substance. Because the supporting information for the ———————— analysis is adequate and the ———————— analysis is a well known analytical technique, it is recommended that the ———————— analysis method not be sent to the FDA labs. This decision is also made with the knowledge that the drug substance specifications remain the same and that there is an adequate method approved for residual solvents.
ADEQUATE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RHÔNE-POULENC

Rhône-Poulenc Rorer

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

January 26, 1999

Federal Express # 5023300866

Lilia Talarico, M.D., Director
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-164**
RP 54563

Lovenox® (enoxaparin sodium) Injection
SUPPLEMENTAL NEW DRUG APPLICATION
DRUG SUBSTANCE CHANGES:
New Source of Heparin sodium (SPL)
Increase Batch Size

NDA NO 20164 REF. NO. 022
NDA SUPPL FOR SCS
SCM 023
SSC 024
Admin Split per CBO

Dear Dr. Talarico:

Reference is made to NDA 20-164, approved March 29, 1993. The purpose of this supplemental NDA is to qualify for the drug substance :

1. an alternative supplier for the starting material heparin sodium, USP
2. an expansion of the approved manufacturing facility at Villeneuve-La-Garenne Plant (project name, ——— ') which is associated with the increased batch size
3. a new regulatory method for residual solvents and clarity testing
4. an increase in the production scale by ———

Heparin sodium, is the starting material used to manufacture enoxaparin sodium drug substance, which is the active ingredient in Lovenox®. The currently approved suppliers for heparin sodium, USP are ——— located in ——— and ——— located in ———. The manufacturing process for heparin sodium, USP at ——— is described in their DMF, number ——. An authorization letter for access to this DMF on behalf of Rhône-Poulenc Rorer was provided in the original NDA 20-164, volume 2.2 page 170. The manufacturing process for heparin sodium, USP at ——— is described in their DMF, number ——. An authorization letter for access to this DMF on behalf of Rhône-Poulenc Rorer was provided in supplement S-004 to the original NDA 20-164, volume 1 page 3-2-2.

ORIGINAL

In order to meet the increased demands for Lovenox® drug product, additional supplies of heparin sodium are required. This supplement provides for an additional supplier for the starting material heparin sodium, USP:

[ ]

The manufacturing process for heparin sodium, USP at — is described in their Type II DMF, number —. An authorization letter for access to this DMF on behalf of Rhône-Poulenc Rorer is included in this submission.

The currently approved site of manufacture for enoxaparin sodium drug substance and the site of the facility extension is:

Rhône-Poulenc Rorer
Villeneuve-La-Garenne Plant
35, Avenue Jean Jaures
92390 Villeneuve-La-Garenne
France

There are no changes to the method of synthesis, or the specifications and analytical methods for the drug substance, enoxaparin sodium. The current release specifications and analytical methods for enoxaparin sodium are identical to those described in supplement S-011, approved on February 24, 1998. A new regulatory method for the determination of residual solvents ——— in enoxaparin sodium has been introduced. This method using ——— techniques, along with the associated validation report is included in this submission. An alternate method for the determination of the clarity of a solution of enoxaparin sodium has been introduced. This method using a ——— method, along with the associated validation report is also included in this submission.

The extension to the approved facility will have a capacity approximately ——— what is currently approved, however, the increased capacity is only related to the [ ] The project to scale up the process is referred to as ——— The qualification of an additional source of heparin sodium, USP, has been performed using this scaled up process.

A comparison of the data obtained from 3 batches of ——— sourced heparin to three batches of heparin from currently approved suppliers demonstrates the — heparin source and the process scale up produce enoxaparin sodium which is comparable to that obtained from approved heparin sources and the current production process. Additionally, a bioequivalence study has been performed demonstrating that the new source of heparin sodium ——— is bioequivalent to the currently approved sources of heparin sodium. The bioequivalence report is included with this submission.

We are providing the pertinent documentation to support a new source of supply for heparin sodium, which is the starting material for the enoxaparin sodium drug substance, and an increase in the batch size for the drug substance in accordance with 21 CFR 314.70(b) (1).

This submission contains an application form FDA 356h, both an archival copy and review copy. This submission contains a User Fee Form. This certifies that a field copy of this submission has been provided to the Philadelphia, PA District Office, the home office of the NDA holder, Rhône-Poulenc Rorer Pharmaceuticals Inc.

If you have any questions concerning this submission please contact the undersigned or Connie Gombatz, (Manager, CMC) at (610)454-5430.

Sincerely,

Dennis Jurgens

Dennis Jurgens
Associate Director, CMC Conformance
Regulatory Affairs

Phone: (610) 454-3364
FAX: (610) 454-2949

Field Copy:

Debra L. Pagano
Philadelphia District Pre-Approval Manager
U.S. Food and Drug Administration
Room 900, U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106-2973

NDA 20-164/S-022, 023, & 024

FEB - 9 1999

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 supplemental application. After preliminary review of the submission, the Agency administratively separated the submission into three supplemental applications as follows:

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

NDA Number: NDA 20-164

Supplement Numbers: S-022, 023, & 024

Therapeutic Classification: Standard

Date of Supplements: January 26, 1999

Date of Receipts: January 27, 1999

These supplements propose the following changes: (S-022) [redacted] as an alternate supplier of the porcine sourced intermediate, heparin sodium; (S-023) the expansion of the Velleneuve-La-Garenne Plant, Villeneuve-La-Garenne, France, and the addition of new equipment to the plant expansion for the production scale-up, by [redacted] in the manufacture of enoxaparin sodium; and (S-024) alternate methods for the enoxaparin sodium specifications "Residual solvents: [redacted] and "Aqueous solution: - clarity".

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 March 28, 1999 in accordance with 21 CFR 314.101(a).

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 yours,

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:
Original NDA 20-164/S-022, 023, 024
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
r/d init: J.Sieczkowski 02/08/99
r/d Init: E.Duffy 02/08/99
DISTRICT OFFICE

Drafted by: KO/February 8, 1999 K. Oliver 02/09/99
Final: KO/02/09/99/c:\mydocuments\NDA20164-02-08-99-S-022-023-024ack-admsplit

SUPPLEMENT ACKNOWLEDGEMENT (AC)