CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-019

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.

Approval Date: March 3, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-019

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-019

APPROVAL LETTER

NDA 20-164/S-019

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 September 9, 1998, received September 11, 1998, 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 September 18, 1998.

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 the addition of a rigid needle shield to cover the approved soft rubber needle shield.

Your submission stated "within thirty (30) days" of the date of your 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,

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-019
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-160/P.Stinavage
HFD-160/P.Cooney
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/February 22, 1999
final: KO/02/22/99/c:\mydocuments\NDA20164-S-019-02-22-99-AP

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-019

CHEMISTRY REVIEW

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

NDA 20-164 SUPPLEMENT: SCP-019 CHEM REVIEW #1 REVIEW DATE: January 5, 1999

SUBMISSION TYPE **DATES**

DOCUMENT	CDER	ASSIGNED	REVIEW
ORIGINAL SS/CBE	09 SEP 1998	16 SEP 1998	----
AMENDMENT BC	18 SEP 1998	24 SEP 1998	----

SUPPLEMENT PROVIDES FOR:
A rigid needle shield (RNS) which is formed by the physical non-bonded addition of a rigid ——— shield over a ——— grey soft rubber needle shield, for the previously approved 0.5 and 1.0 mL HYPAK® SCF® (27G1/2 needle) syringe system.

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 (low molecular weight heparin)
Chem.Type/Ther.Class:

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:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
501	HYPAK® Syringe	Becton Dickinson	Adequate	8-15-97 S-016 Chemistry Report #1	----

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:
Microbiologist's Review of Supplement, October 19, 1998 by P. Stinavage, Microbiologist.

REMARKS/COMMENTS:
1. Microbiologist's conclusion: "The application is recommended for approval on the basis of sterility assurance."
2. LoA to DMF 501 dated November 5, 1998 received as correspondence December 2, 1998.

CONCLUSIONS & RECOMMENDATIONS:
Sufficient and adequate information has been submitted to support the supplemental request to add a rigid needle shield to the previously approved syringe system for the drug product and the supplement should be approved.
The CSO will draft the approval letter.

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

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

cc:
NDA 20-164/SCP-019
HFD-180/L.Talarico
HFD-180/Div File/NDA 20-164
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-181/CSO/K.Oliver
R/D Init by: E.Duffy \
JS/dob DRAFT 1-6-98/Word: n:\wpfiles\chem\S\20164019.1JS

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

"Post Approval" Stability Protocol."

COMMENT:
The submitted stability data complies with the drug product specifications and supports the use of the rigid needle shield (RNS) for the drug product. The post approval stability protocol is adequate for the addition of RNS to the drug product.

Appendix III (pages 65-66).

"Post Approval" Stability Protocol. "

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APPLICATION NUMBER:

NDA 20-164/S-019

MICROBIOLOGY REVIEW

REVIEW FOR HFD-180
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT
19 October 1998

A. 1. NDA 20-164/SCP-019
APPLICANT: Rhone-Poulenc Rorer
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

2. PRODUCT NAMES: Lovenox® (enoxaparin sodium) Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile solution for subcutaneous injection.

4. METHODS OF STERILIZATION:
The drug product is ———————

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is intended for the treatment of deep vein thrombosis or pulmonary embolism.

B. 1. DATE OF INITIAL SUBMISSION: 9 September 1998

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: Original NDA 20-164, DMF 501

4. ASSIGNED FOR REVIEW: 29 September 1998

C. REMARKS: The application provides for the addition of a rigid needle shield, covering the soft rubber needle shield. The only contact that the rigid needle shield makes with the product is the outside contact to the soft rubber shield. The additional shield is not in the fluid path and is not bonded to the inner soft rubber needle shield. The submission is a "Special Supplement - Changes Being Effected".

D. CONCLUSIONS: The application is recommended for approval on the basis of sterility assurance.

Paul Stinavage, Ph.D.

cc: Original NDA 20-164/SCP-019
HFD-180/Div. Files/K. Oliver/J. Sieckowski
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 19 October 1998
R/D initialed by P. Cooney

APPEARS THIS WAY
ON ORIGINAL

E. REVIEW NOTES

The Supplement provides for a rigid needle shield covering the presently approved soft rubber needle shield. The rigid needle shield is not in the fluid path and is not bonded to the inner soft rubber needle shield. The new shield is sterilized ———————————.

A bioburden estimate of the product used in the study was performed using Maximum Likelihood Estimate. Three lots were sampled for bioburden, the results generated were: ——————————————— CFU/item. The presterilization microbial load limit for this product is — CFU/item. The rigid needle shield is sterilized——————————————— ——————————————— to the syringe barrels. The process utilizes the same ———— sterilization process as is currenlty approved.

Validation for sterilization of the rigid needle shield was performed using —— ——————————————— incorporating the minimum acceptable cycle parameters (———— validation cycle vs. ———— process exposure). Three separate validation runs with the syringe barrels with the rigid needle shield were completed. No growth of the challenge organism was detected following exposure in any of the three validation cycles. Routinely, 20 biological indicators will be included in process runs. Presterilization microbial load studies will be performed at least quarterly. Cycle requalification will be performed annually.

Container/closure integrity of the syringe system was assessed by [ ] No contamination of test syringes was detected. Control results were as expected.

Satisfactory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-164/S-019

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-019

Date of Supplement: September 9, 1998

Date of Receipt: September 11, 1998

This supplement proposes the following: the addition of a rigid needle shield to cover the approved soft rubber needle shield.

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 November 10, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 10, 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) 443-0487.

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-019
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Duffy
HFD-180/J.Sieczkowski

DISTRICT OFFICE
Drafted by: KO/September 21, 1998
final: KO/09/21/98
filename: c:\mydocuments\20164-09-21-98-S-019-ackCBE

SUPPLEMENT ACKNOWLEDGEMENT (AC)