CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164/S010

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

MAR 1 8 1997

FINDING OF NO SIGNIFICANT IMPACT

FOR

LOVENOX®
(enoxaparin sodium)
INJECTION

NDA 20-164/S-010

Division of Gastrointestinal and Coagulation Drug Products
HFD-180
Food and Drug Administration
Center for Drug Evaluation and Research

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-164/S-010
Lovenox® (enoxaparin sodium) Injection

Indicated for extended prevention of deep vein thrombosis following hip replacement surgery

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center of Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Lovenox Injection, Rhone-Poulenc Rorer Pharmaceuticals Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (b)(5) which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product.

In support of their supplemental new drug application (S-010), Rhone-Poulenc Rorer has resubmitted the environmental assessment (EA) for S-002, referenced the original EA and provided the following important revisions for the supplement S-010 EA:

1) A new indication has been added for the extended prevention of deep vein thrombosis following hip replacement surgery.

2) Drug product labeling indicates a 40 mg/0.4 mL pre-filled syringe for the new indication.

The new EA information does not present new information on the manufacture of enoxaparin sodium and Lovenox Injection. The manufacturing aspect of the EA remains the same with respect to manufacturing at the approved facilities in that enoxaparin is a depolymerized heparin obtained by alkaline degradation of heparin benzyl ester from porcine mucosa and in that the drug product formulation remains the same.

Approval of the supplemental application will make prophylactic therapy available to a larger group of patients as reflected in the revised indication: Lovenox Injection is indicated for prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip replacement surgery and/or knee replacement surgery. In addition, Lovenox Injection is indicated after hospital discharge for long term prevention of deep vein thrombosis following hip replacement surgery. The drug product will be used in hospital settings for in-patient and out-patient treatment. Disposal is by hospitals as medical waste and returned or damaged product as medical/hazardous waste. The fate and effects of enoxaparin sodium remain unchanged from the original EA.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

APPEARS THIS WAY
ON ORIGINAL

/S/

3-11-97

PREPARED BY:

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Office of New Drug Chemistry II, HFD-820

/S/

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/S/

3/18/97

APPROVED:
Nancy B. Sager
Environmental Scientist, HFD-357
Center for Drug Evaluation and Research

Attachments:
Environmental Assessment Material Safety Data Sheet (Drug Substance).

2.4.2 Environmental Assessment : FOI Version

Environmental Assessment for Lovenox® Injection sNDA
Non-confidential (FOI) Version

Section 1: Date March 14, 1996

Section 2: Applicant Rhône-Poulenc Rorer

Section 3: Address 500 Arcola Road
Collegeville, PA

Section 4: Description of Proposed Action

a) Requested Approval

Rhône-Poulenc Rorer is submitting a supplementary new drug application for a new indication for Lovenox®, the prevention of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing: hip or knee replacement surgery; or long term prophylaxis following hip replacement surgery. The original NDA for Lovenox®, #20-164, was approved on March 29, 1993. The drug product for this new indication remains the same as that for the currently marketed Lovenox® Injection, a prefilled syringe. For the new indication which is the subject of this application, the prefilled syringe will have a fill volume of 0.4 ml, representing 40 mg of enoxaparin (0.4 ml of 100mg/ml enoxaparin solution).

Complete environmental assessment information was filed with the original NDA #20-164 and updated with a sNDA on August 23, 1994. All information which pertains to the enoxaparin drug substance, the drug product and the production is the same as that contained in the previous filing. A fifth year market projection, for the United States, for all Lovenox®, the subject of this application and all current and expected approved indications, gives a total product quantity of "Confidential" pre-filled syringes. This represents "Conf." Kg of enoxaparin drug substance. From this quantity the expected introduction concentration (EIC) is calculated to be "Confidential" ppm or "Conf." ppt. As this represents a level for the EIC, the Tier O approach is adopted for this sNDA and no further new information is provided for format items 7 to 14 and 15. The following addresses each of the remaining format items for an Environmental Assessment and identifies those items which do or do not differ from the original EA including the updated EA of August 23, 1994.

b) Need for Action

Clinical studies have demonstrated that Lovenox® offers protection in the prevention of deep vein thrombosis in patients undergoing: hip or knee replacement, or long term prophylaxs following hip replacement surgery. Approval of this sNDA would make this therapy available to patients at risk after these surgical treatments.

c) Production Locations

The drug substance and drug product will be manufactured, packaged and labeled in the same facilities as previously described for the existing Lovenox® product. The facilities are addressed in the previous complete EA Section 4.C. (see Attachment I for the complete updated EA of August 23, 1994).

d) Locations of Use

As with the existing Lovenox® product the subject of this application will be used in hospitals for in-patient use through out the United States.

e) Disposal Sites

Disposal of Lovenox® drug product and returned goods will be carried out as previously described in the full EA Section 4.d from August 23, 1994 (see Attachment I).

Section 5: Identification of Chemical Substances that are the Subject of the Proposed Action

All aspects of Section 5 related information for the Lovenox® Injection product are the same as that previously filed with the complete updated EA of August 23, 1994 (see Attachment I, Section 5 and the referenced Appendix).

Section 6: Introduction of Substances into the Environment

a to c)

All aspects of Lovenox® Injection product related to format items 6.a to 6.c are the same as provided in the complete updated EA of August 23, 1994 (see Attachment I, Section 6 and referenced Appendices).

d) Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Due to the low utilization rate of RPR facilities for Lovenox® (see Attachment I, Section 8) and the nature of the Lovenox® product the incremental change at the manufacturing sites as a result of approval of this sNDA will not have a significant impact on our ability to meet current emission requirements.

e) Expected Introduction Concentration

Calculations were performed to estimate the concentration of enoxaparin sodium that could be present in the United States as a result of the use of the Lovenox® Injection product. The result of those calculations is expressed below as the Expected Introduction Concentration (EIC). The estimate assumes that all enoxaparin sodium from the Lovenox® Injection product for the United States will be administered to patients and disposed of directly into sewage systems. This over estimates the introduced concentration in at least two ways; one it assumes none of the product is left un-sold or expires and is returned for disposal outside sewage treatment systems, secondly, it assumes that all enoxaparin sodium consumed from Lovenox® Injection is excreted into sewage treatment systems. Patient metabolism will reduce the amount of Enoxaparin sodium reaching the environment. None the less, the EIC for Enoxaparin sodium has been calculated to be "Confidential" ppm or "Conf." ppt. The EIC is calculated based upon a fifth year market estimate which includes the Lovenox® from all current approved applications and all applications expected to be approved five years from now. That market estimate represents "Conf." Kg of enoxaparin drug substance. Using the proposed method of calculation of the EIC (for the Expected Introduction Concentration from use) gives the EIC of "Conf." ppt.

Proposed EIC Calculation

$$\text{EIC - aquatic (ppm)} = A \times B \times C \times D$$

where A = Kg/year production
B = 1/liters per day entering POTW's *
C = year/365 days
D = 10^6 mg/Kg

* 1.115×10^{11} liters per day

This calculation shows that the EIC for Lovenox® Injection which is the subject of this application is far level and therefore the Tier 0 approach is claimed for this sNDA and no new data is provided for format items 7, 8, 9, 10, 11 and 15.

Section 7: Fate of Emitted Substances in the Environment

The information for format item 7 does not differ from that already provided in the complete EA of August 23, 1994 (see Attachment I, Section 7)

Section 8: Environmental Effects of Released Substances

The information for format item 8 does not differ from that provided in the complete EA of August 23, 1994 (see Attachment I, Section 8).

The incremental increase anticipated in production and use of Lovenox® Injection as a result of approval of this sNDA does not increase the EIC to the 1 ppb level (calculated EIC = "Conf." ppt). Therefore, the result of approval of this sNDA will not have a significant environmental impact as a result of the increased use of Lovenox® Injection.

Section 9: Use of Resources and Energy

Information for format item 9 does not differ from that provided in the complete EA of August 23 1994 (see Attachment I, Section 9).

Section 10: Mitigation Measures

Information for format item 10 does not differ from that provided in the full EA of August 23, 1994 (see Attachment I, Section 10).

Section 11: Alternatives to the Proposed Action

Basic information for format item 11 does not differ from that provided in the complete EA of August 23, 1994 (see Attachment 1, Section 11).

The alternative to the proposed action requested in this sNDA is non-approval. The non-approval of this sNDA will prevent patients in the United States from receiving the beneficial effects of treatment with Lovenox® Injection after surgical knee or hip replacement.

Section 12: List of Preparers

In addition to the list of preparers provided in the complete EA of August 23, 1994, the following person is added to the list.

William Studt (Ph.D. Synthetic Organic Chemistry)
Process Chemistry & Biochemistry
Regulatory Documentation
Rhône-Poulenc Rorer
Collegeville, PA

Section 13: **Certification**

Attachment II contains the certification as to the veracity of this document.

Section 14: **References**

Information for format item 14 does not differ from the complete EA provided August 23, 1994 (see Attachment I, section 14).

Section 15: **Appendices**

Information for format item 15 differs from the complete EA provided August 23, 1994 (see Attachment I, Section 15 and the Appendices related to format items 1 to 6 of the complete EA) only in the addition of a certification as to the veracity of this document (see Attachment II).

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31 Page(s) Redacted

Attachment 1
EA for NDA 20164
(S002)

Appendix II

Enoxaparin Drug Substance:
Physical and Chemical Characteristics

Material Safety Data Sheets:
Enoxaparin
Lovenox® Injection

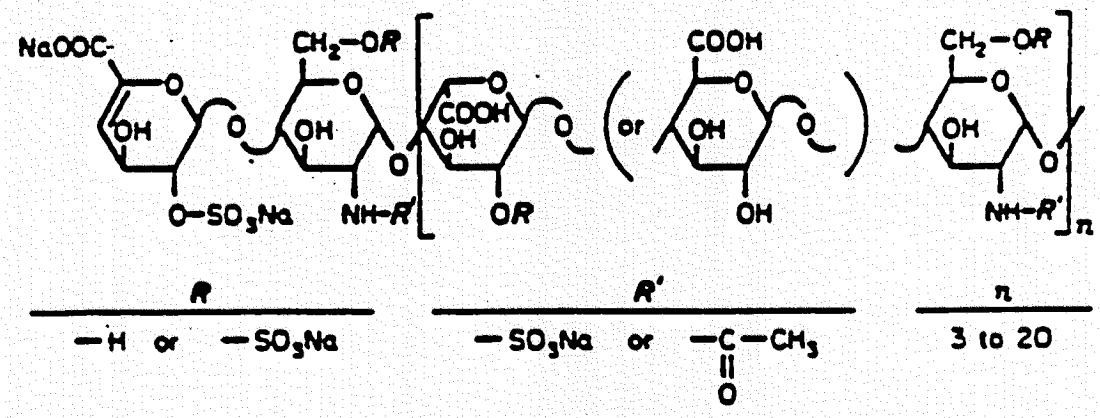
Packaging Specifications

Appendix II

Enoxaparin Drug Substance
Physical and Chemical Characteristics

Name:	Enoxaparin
CAS Reg. No.:	Not available
Molecular Weight:	Mean - 4500 Range - 3500 to 5550
Physical Description:	White to slightly white-yellowish, odorless powder
Additives:	None
Residuals:	Benzyl alcohol and benzethonium, Residual Solvents: Methanol/Methylene Chloride

Structural Formula:



R	R'	n
—H or —SO_3Na	—SO_3Na or —C(=O)—CH_3	3 to 20

[Pharmaceutical information]

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Translated from French