

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164, S015

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

NDA 20-164

Page 6

ENVIRONMENTAL ASSESSMENT

AND

JUL 26 1997

FINDING OF NO SIGNIFICANT IMPACT

FOR

**LOVENOX®
(enoxaparin sodium)
INJECTION**

NDA 20-164/S-015

**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-015
Lovenox® (enoxaparin sodium) Injection

Indicated for the treatment of deep vein thrombosis and pulmonary embolism.

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 to 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)~~^{NS} 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-015), Rhone-Poulenc Rorer has referenced the environmental assessment (EA) for S-002, referenced the original EA and provided the following important revisions for the supplement S-015 EA:

1. A new indication for the treatment of deep vein thrombosis and pulmonary embolism.
2. The addition of calibrated prefilled syringes of drug product, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1.0 mL, for the new indication.

The new EA information does not present new significant 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.

The 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: "The prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip or knee replacement surgery. The treatment of deep vein thrombosis and pulmonary embolism." 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.

BEST POSSIBLE

APPEARS THIS WAY ON ORIGINAL

7-10-97
DATE

/S/ [REDACTED]

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7/11/97
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7/26/97
DATE

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APPROVED: [REDACTED]
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Center for Drug Evaluation and Research

Attachment:
Environmental Assessment Material Safety Data Sheet (Drug
Substance).
Environmental Assessment FOI version.

Lovenox® (enoxaparin sodium) Injection

ENVIRONMENTAL ASSESSMENT

DEEP VEIN THROMBOSIS

FOI VERSION

b) Need for Action

Approval of this sNDA for Lovenox® Injection, 60 mg, 80 mg and 100 mg Prefilled Syringes will make these drug product presentations available for use in the clinically demonstrated prevention of deep vein thrombosis.

c) Production Locations

The drug substance will be manufactured in the same facilities as previously described for the existing Lovenox® Injection product. The facilities identified in the previous complete EA Section 4.C. for the drug substance are:



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

The 60 mg, 80 mg and 100 mg Prefilled Syringe drug products will be manufactured, packaged and labeled at the same facilities as previously described for the existing Lovenox® Injection product. The facilities identified in the previous complete EA Section 4.C. for the drug product are:

Rhône-Poulenc Rorer
Maisons-Alfort
180, Rue Jean Jaures
94700 Maisons-Alfort
France

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.

At US hospitals, pharmacies and clinics, empty or partially empty packages of the drug product will be disposed of according to the hospital, pharmacy or clinic procedures.

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. Information on the Enoxaparin drug substance and the related MSDS's from the August 23, 1994 Environmental Assessment are included here for reference as Attachment I.

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 for the enoxaparin sodium drug substance are the same as provided in the complete updated EA of August 23, 1994.

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

Due to the low utilization rate of RPR facilities for Lovenox® 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 used as a result of the approval of this application for the 60 mg, 80 mg and 100 mg Prefilled Syringe drug product, and related applications for the same drug product, has been calculated to be "CONF" ppm or "CONF" ppt. The EIC from use is based upon the projected use of "CONF" Kg of enoxaparin sodium as a result of the applications for use of the 60, 80 and 100 mg drug product presentations. The EIC calculated based upon a total fifth year market estimate which includes the Lovenox® from all current approved applications and all applications expected to be approved five years from now is "CONF" ppm or "CONF" ppt. That market estimate for all drug product presentations 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 for the total enoxaparin sodium use and "CONF" ppt for the enoxaparin sodium use resulting from this drug product presentation.

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