

Dr. Stephen B. Fredd
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February 28, 1997
NDA 20-164



September 26, 1994 a meeting was held to discuss several clinical studies with Lovenox. It was agreed that study 528 (an open phase II study) would be included as supportive, while a second pivotal study would be required in addition to PK 529. The RPR minutes to this meeting were submitted to the Agency on October 19, 1994 and the agency's minutes were issued on January 31, 1995.

In accordance with 21 CFR 314.50 and 314.71, this application contains information limited to that needed to support the additional indication. The following technical sections are provided: 1) Chemistry, Manufacturing and Controls, 2) Human Pharmacokinetics and Bioavailability, 3) Clinical Data and 4) Statistics. Other information concerning Lovenox is provided in the technical sections provided in the approved New Drug Application (NDA 20-164).

Two adequate and well-controlled (one open label - CPK 2091; one partially blinded (enoxaparin dosing regimen) - PK 529) multicenter studies have been conducted in Canadian, European and US centers as well as centers in Australia and Israel. These studies compared the efficacy and safety of enoxaparin at doses of 1.0 mg/kg twice a day (studies CPK 2091 and 529) or 1.5mg/kg once a day (study 529) administered subcutaneously and unfractionated heparin administered intravenously in the treatment of lower extremity deep vein thrombosis (study CPK 2091 and study 529), and lower extremity deep vein thrombosis associated with pulmonary embolism (study 529). The primary efficacy outcome variable was the incidence of recurrent venous thromboembolic disease within three months of randomization. Patients with symptoms or signs of recurrent venous thrombosis underwent objective testing using a combined approach of impedance plethysmography, duplex ultrasonography and venography. Patients suspected of having pulmonary embolism were to undergo a lung scan or a pulmonary angiography.

The results demonstrate that 1.5 mg/kg qd SC or 1.0 mg/kg q12h SC enoxaparin was as effective as unfractionated heparin in the treatment of deep vein thrombosis with or without pulmonary embolism.

PROPOSED REVISION TO THE INDICATION:

Lovenox Injection is indicated for

DRAFT LABELING

A large black rectangular redaction box covering the text of the proposed revision to the indication.

PROPOSED REVISION TO DOSAGE AND ADMINISTRATION

DRAFT LABELING

A large black rectangular redaction box covering the text of the proposed revision to dosage and administration.

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Qualification of New Syringes: Graduations, Size, Fill Volumes
Qualification of New Manufacturing Line

This indication may require treatment with up to 1.5mg/kg Lovenox Injection. For this reason new 1ml graduated syringes filled with either 60, 80, or 100 mg of the previously approved 100 mg/ml formulation are also submitted with this supplemental NDA.

Supporting information to qualify the new manufacturing line (line 4) in [REDACTED] for these syringes is also included in this submission. This line is similar to the currently approved lines 1 and 3, with differences present only in the number of filling heads per line and the degree of automation of the visual inspection. Please note that both lines 1 and 3 at the [REDACTED] site were recently inspected (April 25-May 3, 1996) by Dr. David Pulham of the Phoenix branch, FDA. Corrections to all issues mentioned in the FDA 483 report have been initiated. It should be noted that the use of line 3 as an alternate manufacturing line for the 30 mg pfs, which was the subject of S-012, received approval on October 23, 1996.

The formulation used for the 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/1.0 mL pre-filled syringes is the same as the currently approved Lovenox 30 mg/0.3mL pre-filled syringe, 100 mg/mL solution of enoxaparin sodium for injection. The three new products will be used to support the new indication. The specifications for the 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/1.0 mL pre-filled syringes are the same or proportionally similar to those for the already approved 30 mg/0.3 mL pre-filled syringe.

Due to the volume increase of injectable solution, 1.0 mL syringes will be used with the 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/1.0 mL product as opposed to the 0.5 mL syringe used with the currently approved 30 mg product. This new 1.0 mL calibrated syringe is manufactured by the same company [REDACTED] uses components manufactured from the same raw materials, and meets the same, or proportional, specifications as the previously approved 0.5 mL syringe.

Stability data on 3 lots each of the 60 mg/0.6 mL and 100 mg/1.0 mL products are included. No testing was performed on 80 mg/0.8 mL drug product, which is consistent with the discussions held between RPR and FDA that allowed bracketing to be used for these stability batches. This bracketing agreement was proposed in a letter to the Agency on April 11, 1996 and confirmed in an additional correspondence dated May 17, 1996. For the 6 lots of drug product tested, 3 months stability data are included. The twelve month stability data is expected to be submitted in August, 1997.

Other Information:

The proposed package insert is provided in WordPerfect 6.0 format as an attachment to this letter for ease of review; a hard copy of the file is also attached. It should be noted that the proposed labeling uses the currently approved labeling, version L, as the point of comparison for labeling changes.

In accordance with the Prescription Drug User Fee Act of 1992, a check (Check No. [REDACTED] in the amount of [REDACTED] was sent to the Food and Drug Administration, Pittsburgh, PA on December 18, 1995. The application was assigned the User Fee Identification Number [REDACTED]

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As required by section 306(k) (1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k) (1)], we hereby certify that, in connection with this application, Rhone-Poulenc Rorer did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the act.

Please note that a copy of the CMC section of this submission has been sent to Ms. Debra Pagano of the Philadelphia District Office.

As cited under 21CFR314.108(b)(5), we have included a request for patent exclusivity with this supplemental NDA.

Rhône-Poulenc Rorer Pharmaceuticals Inc. considers the information in this application to be confidential and proprietary and we request that no portions thereof be disclosed to third parties, under FOI or otherwise, without first obtaining written permission from Rhône Poulenc Rorer.

Should you have any questions or require any additional information during the review of this application, please contact me at (610) 454-3023.

Sincerely Yours,

A handwritten signature in cursive script, appearing to read 'Thomas E. Donnelly, Jr.'.

Thomas E. Donnelly, Jr., Ph.D.
Group Director
Worldwide Regulatory Affairs

TED/bh
Attachment

Copy to Ms. Pagano
Philadelphia District Office

APPEARS THIS WAY ON ORIGINAL

Item 13. Patent Information

- | | |
|-------------------------|--|
| 1) Patent number | 4,486,420 |
| 2) Date of expiration | December 4, 2001 |
| 3) Type of patent | Process, drug, drug product and method of use. |
| 4) Name of patent owner | Choay, S.A. |
| 5) U.S. representative | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

The undersigned declares that Patent No. 4,486,420 covers the process of preparing, formulation, composition, and method of use of Applicant's Lovenox® (enoxaparin sodium) product. This product is the subject of this application for which approval is being sought.

Signed:

Name:

Title:


Ross J. Oehler

Assistant General Counsel, Patents and Trademarks
Rhône-Poulenc Rorer Pharmaceuticals Inc.

Date: 12/4/96


APPEARS THIS WAY ON ORIGINAL

Item 13. Patent Information

- | | |
|-------------------------|--|
| 1) Patent number | 4,692,435 |
| 2) Date of expiration | December 24, 2004 |
| 3) Type of patent | Process, drug, drug product and method of use. |
| 4) Name of patent owner | Choay, S.A. |
| 5) U.S. representative | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

The undersigned declares that Patent No. 4,692,435 covers the process of preparing, formulation, composition, and method of use of Applicant's Lovenox® (enoxaparin sodium) product. This product is the subject of this application for which approval is being sought.

Signed:
Name:
Title:



Ross J. Oehler
Assistant General Counsel, Patents and Trademarks
Rhône-Poulenc Rorer Pharmaceuticals Inc.

Date: 12/4/96

APPEARS THIS WAY ON ORIGINAL

Item 13. Patent Information

- | | |
|-------------------------|--|
| 1) Patent number | 5,389,618 |
| 2) Date of expiration | February 14, 2012 |
| 3) Type of patent | Process, drug, drug product and method of use. |
| 4) Name of patent owner | Rhône-Poulenc Rorer S.A. |
| 5) U.S. representative | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

The undersigned declares that Patent No. 5,389,618 covers the process of preparing, formulation, composition, and method of use of Applicant's Lovenox® (enoxaparin sodium) product. This product is the subject of this application for which approval is being sought.

Signed:

Name:

Title:


Ross J. Oehler

Assistant General Counsel, Patents and Trademarks
Rhône-Poulenc Rorer Pharmaceuticals Inc.

Date: 12/4/96

APPEARS THIS WAY ON ORIGINAL



Supplemental New Drug Application:#20-164

RHÔNE-POULENC RORER PHARMACEUTICALS INC Form FDA 356h

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

Item 13 and Item 14

Lovenox®
(enoxaparin sodium)

Item 14: Patent Certification


Item 14 for Patent Certification for LOVENOX ® (enoxaparin sodium) Supplemental New Drug Application is found on the following pages.

APPEARS THIS WAY ON ORIGINAL

Item 14: Patent Certification



Item 14 - Patent/Exclusivity Information

- 1) Active Ingredient(s): enoxaparin sodium
- 2) Strength(s): 60 mg/0.6 ml; 80 mg/0.8 ml
100 mg/1 ml (prefilled 1 ml syringe)
- 3) Trade Name: LOVENOX®
- 4) Dosage Form (Route of Administration): Subcutaneous injection
- 5) Application Firm Name: Rhône-Poulenc Rorer Pharmaceuticals Inc.
- 6) IND Number: 
- 6) NDA Number: 20-164
- 7) Approval Date: n/a
- 8) Exclusivity -- date first ANDA could be submitted or approved and length of exclusivity period: Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this application.
- 9) Applicable patent numbers and expiration date of each:
4,486,420 exp. December 4, 2001
4,692,435 exp. December 24, 2004
5,389,618 exp. February 14, 2012
- 10) To the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is attached. We have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application. The reasons that these studies or reports are insufficient are presented in the attachment as well.



Attachment to Patent/Exclusivity Information

The published studies and reports presented in the clinical data section (publications) are insufficient as a basis for approval of Lovenox in the treatment of deep vein thrombosis. The pivotal studies contained in this supplemental NDA are the only available studies which sufficiently demonstrate the efficacy of Lovenox in the treatment of patients with deep vein thrombosis.

MEMORANDUM OF TELECON

DATE: December 29, 1998

TIME: 1:30pm-3:00pm

APPLICATION NUMBER: NDA 20-164/S-015; Lovenox® (enoxaparin sodium) Injection

BETWEEN:

Name: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Robert W. Babilon, Associate Director, Regulatory Affairs Liaison
Cheryl Troilo, Manager, Regulatory Affairs Labeling
Gerry Rhodes, Ph.D., Senior Director, Drug Metabolism
Janet Rush, M.D., Vice President, Cardiovascular Research

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Lilia Talarico, M.D., Division Director
Karen Oliver, RN, MSN, Regulatory Health Project Manager

Division of Clinical Pharmacology and Biopharmaceutics, HFD-870

John Hunt, B.Sc., Deputy Director
Arzu Selen, Ph.D., Biopharmaceutics Reviewer

Phone: 610-454-3047

SUBJECT: NDA 20-164/S-015, Lovenox® (enoxaparin sodium) Injection: Labeling and Phase IV Commitments

BACKGROUND:

This supplemental new drug application provides for the use of Lovenox® (enoxaparin sodium) Injection for: (1) the inpatient treatment of acute deep vein thrombosis with and without pulmonary embolism, when administered in conjunction with warfarin sodium; and (2) the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium. An approvable letter was issued February 27, 1998. The sponsor responded to the approvable letter with a series of submissions (May 19 and 28, June 12, July 6, September 24, and October 8, 1998) containing additional biopharmaceutical and labeling information.

In a December 28, 1998 correspondence, the sponsor requested a teleconference to discuss labeling issues and any Phase IV commitments relevant to S-015. The User Fee Goal date for this application is January 7, 1999.

TELEPHONE CALL:

After mutually satisfactory discussion, the Agency and the sponsor agreed to the wording for the package insert (see Attachment 1).



The call was concluded.

APPEARS THIS WAY ON ORIGINAL

/s/

12/30/98

Karen Oliver, RN, MSN
Regulatory Health Project Manager

/s/

12-31-98

Lilia Talarico, M.D.
Division Director

Attachment: Labeling Text

Oliver

NDA 20-164/S-015

" 21 1998

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
500 Arcola Road
P.O. Box 5096
Collegeville, PA 19426-0800

" 21 1993

Dear Dr. Donnelly:

We acknowledge receipt on July 7, June 15, and May 29 and 20, respectively, of your July 6, June 12, and May 28 and 19 resubmissions to your supplemental new drug application for Lovenox® (enoxaparin sodium) Injection.

These resubmissions contain additional biopharmaceutics and labeling information submitted in response to our February 27, 1998 action letter.

With these amendments, we have received a complete response to our action letter.

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, 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