

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-058

Name: Lovenox (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals, Inc.

Approval Date: April 21, 2004

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APPLICATION NUMBER:
NDA 20-164/S-058

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APPLICATION NUMBER:

20-164/S-058

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-058

Aventis Pharmaceuticals
Attention: Christine Chansky, M.D., J.D.
Director, Regulatory Liaison
Global Drug Regulatory Affairs
200 Crossing Blvd.
Bridgewater, NJ 08807

Dear Dr. Chansky:

Please refer to your supplemental new drug application dated November 14, 2003, received November 17, 2003, 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 deletion of the one point ampule from the **DESCRIPTION, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the package insert.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the revisions listed below.

1. Incorporate the revisions made in S-048 (submitted August 9, 2002, received August 12, 2002, approved on draft December 18, 2003).
2. Incorporate the revisions made in S-056 (submitted October 10, 2003, received October 14, 2003, approved on draft April 13, 2004).
3. In the **PRECAUTIONS** section, Laboratory Tests subsection, in the first paragraph, fourth sentence that begins, "If during Lovenox Injection therapy . . ." the term "Pharmacodynamics" should be revised to "Pharmacokinetics" so that the sentence reads "If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**)."

The final printed labeling (FPL) must be identical, except for the revisions indicated above, to the submitted labeling (package insert submitted November 14, 2003) and must be formatted in accordance with the requirements of 21 CFR 201.66. These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-058." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joyce Korvick
4/21/04 01:17:54 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-058

LABELING REVIEW(S)

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SLR-058

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals, Inc.

Materials Reviewed: package insert (PI).

Submission Date: November 14, 2003

Receipt Date: November 17, 2003

Background and Summary

BACKGROUND

Aventis submitted Annual report Y-008 on September 21, 2001. During review of the report, it was noticed that the ampules used in the manufacture of this product have been changed to include a one-point cut (OPC) and that the design and text of the carton for the ampules have been changed. On November 2, 2001, the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) sent Aventis a supplement request letter requesting that they submit a "Special Supplement – Changes Being Effected" supplemental application within 30 days. The application should contain the following:

- Complete, clear and concise instructions and diagrams (if necessary) on the carton and in the **DOSAGE** and **ADMINISTRATION** section of the package insert concerning the proper technique to be used when opening the one-point cut ampules.
- Ampule carton labeling revisions such that the carton is compliant with the labeling regulations identified in 21 CFR 201.1, 201.5, 201.10, 201.15, 201.17, 201.18, 201.50, 201.51, and 201.55.
- All labeling components related to the OPC ampule, e.g., instruction sheets, detailing materials.
- Complete chronology of all ampule changes as well as samples of all ampules previously and currently used.

Aventis submitted Supplement _____ as a "Changes Being Effected" _____ supplement on _____ and received on _____, to provide for _____

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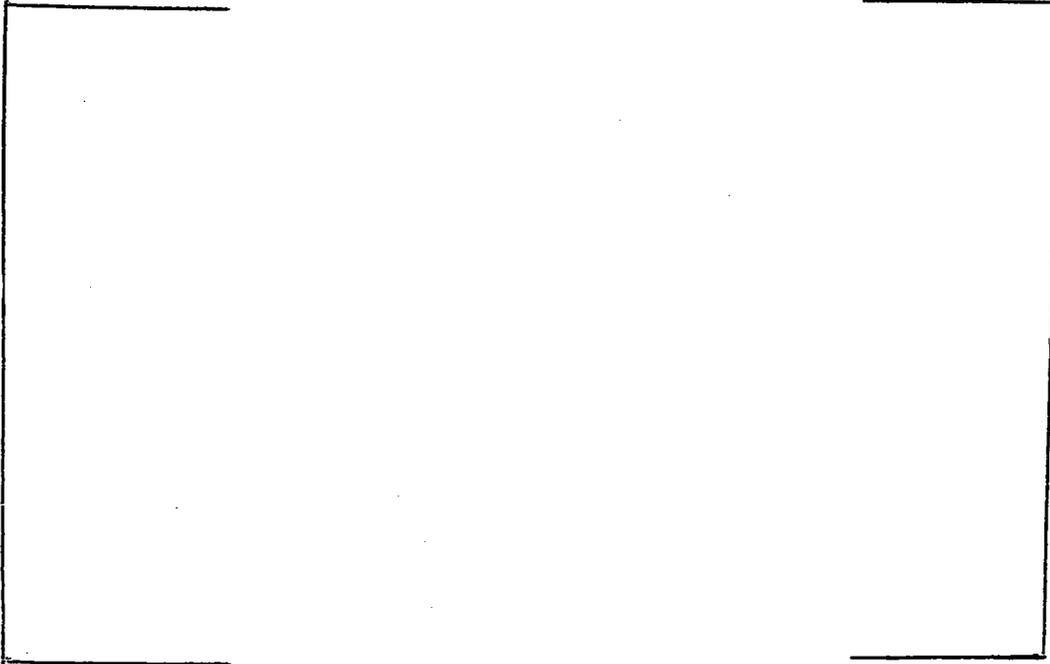
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of trade secret and/or

confidential commercial

information from

20-164 / S-058 LABELING REVIEW



On August 30, 2002, DGCDP sent Aventis an approvable letter to S-043 (submitted May 15, 2001, received May 16, 2001, not approved September 14, 2001, resubmitted May 1, 2002, received May 2, 2002, approvable August 30, 2002, resubmitted September 20, 2002, received September 23, 2002, approved January 23, 2003).

On January 17, 2003, Aventis submitted a general correspondence to Supplement SCM-043 (S-043) (submitted May 15, 2001, received May 16, 2001, not approved September 14, 2001, resubmitted May 1, 2002, received May 2, 2002, approvable August 30, 2002, resubmitted September 20, 2002, received September 23, 2002, approved January 23, 2003), in which they responded to issues delineated in the August 30, 2002, approvable letter to S-043. The issues surrounding the carton and immediate container labeling from _____ were addressed in S-043. The issue regarding the use of the OPC ampule in the PI remained unresolved. Items 2.a., 2.b., and 2.c. in the _____ were relevant to the labeling proposed in S-043, so the sponsor submitted the letter to S-043. In the sponsor's January 17, 2003, letter, the sponsor referenced an _____ that was submitted on page 19 in the original submission to _____. Aventis also stated that "Aventis hereby commits to continue providing education and training to health care professionals using the One Point Cut ampule. It is important to note that the One Point Cut ampule represents less than ~% of the entire Lovenox line used in the United States." Aventis also stated that "In compliance with cGMP 21 CFR part 211 (21 CFR 211.198) Aventis maintains a data base of technical complaints that includes instances of ampule breakage or problems with opening the ampules. Thirdly, the sponsor responded that the primary basis for the switch from Break Ring to One Point Cut (OPC) ampule was to eliminate defects caused during _____ testing of the ampules, which resulted in the ceramic Break Ring becoming discolored (changed from white to pink). These defects slow down the

inspection and processing procedures for Lovenox Ampules. In addition, there are other advantages to the OPC ampule, including: 1) a reduction in the opening force necessary for the OPC ampule relative to the Break Ring ampule; 2) there is less glass particulate matter produced during opening an OPC ampule versus the Break Ring ampule; and 3) OPC ampules are less susceptible to breakage during processing and transportation due to their design.”

On _____ Aventis withdrew supplement _____ and informed the Agency that production of the Lovenox 30 mg One Point Cut (OPC) ampule has been discontinued. No additional Lovenox ampule dosage forms are planned.

On August 9, 2002 (received August 12, 2002), Aventis submitted SLR-048 (S-048) to revise the current Lovenox prescribing information based on the findings provided in the final study reports for the Weight-Dependent Effect protocol (Study RP54563Q-150) and the Renal Impairment protocol (Study RP54563Q-146). DGCDP sent the sponsor an approvable letter on February 13, 2003. The sponsor responded to the approvable letter on August 12, 2003 (received August 12, 2003). The S-048 was approved on draft labeling on December 18, 2003.

On November 14, 2003 (received November 17, 2003), Aventis submitted SLR-058 (S-058) providing for changes in the labeling section of the approved New Drug Application for Lovenox. Specifically, to delete the one point ampule from the **DESCRIPTION, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the approved labeling. Supplement S-048 was approved one month after S-058 was submitted. Therefore, the labeling submitted to S-058 did not incorporate the revisions approved in S-048.

Review

PACKAGE INSERT

The package insert proposed for S-058, dated November 14, 2003 (received November 17, 2003), identification number 50070790 (DSM Pharmaceuticals) and identification number 50070788 (Le Trait) were compared to labeling approved on draft from Supplement S-048 dated August 12, 2003 (no identifier number). The submitted package inserts are identical to the approved package insert except for the following:

I. **DESCRIPTION** section

- A. In the second paragraph that begins “Lovenox Injection is available . . .” the sponsor deleted the fifth line that reads “-Ampules 30 mg/0.3 mL”

This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

- B. In the sixth paragraph, first sentence that begins “The Lovenox prefilled syringes . . .” the sponsor added the word “and” after the word “syringes” and deleted the words “and ampules” after the second word “syringes” so that the sentence reads “The Lovenox prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection.”

This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

- C. The sponsor has not incorporated the revisions approved in S-048 (submitted August 9, 2002; received August 12, 2002, amended August 12, 2003; received August 13, 2003; approved on draft labeling on December 18, 2003) in the **CLINICAL PHARMACOLOGY** section of the PI (see September 25, 2003 RPM review to S-048).

Supplement S-048 was approved one month after S-058 was submitted. Therefore, the labeling submitted to S-058 did not incorporate the revisions approved in S-048. The sponsor should incorporate the revisions to the DESCRIPTION section of the PI approved in S-048 on December 18, 2003, into the labeling for S-058.

II. PRECAUTIONS section

The sponsor has not incorporated the revisions approved in S-048 (submitted August 9, 2002; received August 12, 2002, amended August 12, 2003; received August 13, 2003; approved on draft labeling on December 18, 2003) into the **PRECAUTIONS** section of the PI (see September 25, 2003 RPM review to S-048).

Supplement S-048 was approved one month after S-058 was submitted. Therefore, the labeling submitted to S-058 did not incorporate the revisions approved in S-048. The sponsor should incorporate the revisions to the PRECAUTIONS section of the PI approved in S-048 on December 18, 2003, into the labeling for S-058.

III. DOSAGE AND ADMINISTRATION section

- A. In the third paragraph, item number 1., that begins “**1. 100 mg/mL Concentration:**” the sponsor deleted the phrase “30 mg/0.3 mL ampules” so that the sentence reads “**1. 100 mg/mL Concentration** 30 mg/0.3 mL and 40 mg/0.4 mL prefilled single-dose syringes, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1 mL prefilled, graduated, single-dose syringes, 300 mg/3.0mL multiple-dose vials.”

This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

- B. **Adult Dosage** subsection, *Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism* sub-subsection

Supplement S-048 was approved one month after S-058 was submitted. Therefore, the labeling submitted to S-058 did not incorporate the revisions approved in S-048. The sponsor should incorporate the revisions to the DOSAGE and ADMINISTRATION section of the PI approved in S-048 on December 18, 2003, into the labeling for S-058.

- C. In the **Administration** subsection, in the second paragraph, first sentence that reads “The use of a tuberculin syringe or equivalent is recommended when using Lovenox ampules or multiple-dose vials to assure withdrawal of the appropriate volume of drug,” the sponsor deleted the phrase “ampules or” so that the sentence reads “The use of a tuberculin syringe or equivalent is recommended when using Lovenox multiple-dose vials to assure withdrawal of the appropriate volume of drug.”

This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

- D. Following the **Administration** subsection, following the *Subcutaneous Injection Technique* sub-subsection, the sponsor deleted the following **Directions for use of One Point Cut (OPC) ampules for Lovenox Injection** sub-subsection:

“Directions for use of One Point Cut (OPC) ampules for Lovenox Injection.

Use aseptic technique throughout the process. Prior to starting, gently tap the top of the ampule to assist the flow of the solution from the upper portion of the ampule to the lower portion.

1. Locate the yellow dot on the upper portion of the ampule. Below this dot is a small score on the neck of the ampule. Hold the ampule with the yellow dot **facing away from you**. *Do not try to break the ampule at the colored rings*, which are identification marks used only in manufacturing.
2. Cover yellow dot with your index finger and position your thumb opposite yellow dot.
3. Apply pressure to the top and bottom portions of the ampule to snap the ampule open away from you.”

This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

IV. HOW SUPPLIED section

- A. In the first table titled “100 mg/mL Concentration” the sponsor deleted the first line under the header row that read as follows:

Ampules 30 mg/0.3 mL	3000 IU	10 ampules	Medium Blue	0624-03
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This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

- B. In footnote 1 under the table “100 mg/mL Concentration” in the second sentence that begins, **Lovenox Injection . . .**” the sponsor deleted the word “ampules” after the phrase “**Lovenox Injection**” so that the sentence reads “**Lovenox Injection** 30 and 40 mg prefilled syringes, and 60, 80 and 100 mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection.**”

This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

- C. Following the second table titled “150 mg/mL Concentration” the sponsor deleted the fourth sentence that reads “Lovenox Injection ampules manufactured by: Aventis Pharma LTD Dagenham Essex RM10 7XS United Kingdom.”

This removes the reference to the discontinued 30 mg/0.3 mL ampule from the section. The deletion is acceptable.

- D. In the seventh sentence that reads “©2002 Aventis Pharmaceuticals Inc. Rev. July 2003” the sponsor revised the date to “September 2003” so that the sentence reads “©2002 Aventis Pharmaceuticals Inc. Rev. September 2003.”

The revision is editorial and acceptable.

CONCLUSIONS

1. **The following revisions are acceptable: I.A.-B., III.A., III.C., III.D., and IV.A.-C.**
1. **The following editorial revision is acceptable: IV.D.**
3. **The sponsor should incorporate the revisions approved in S-048 on December 18, 2003, into the labeling for S-058 from items I.C., II., and III.B.**
4. **Supplement S-058 should be approved on draft with the revisions approved in S-048 incorporated in the final printed labeling to S-058.**

NDA 20-164/S-058

RPM Review

Page 8

Diane Moore, B.S.
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted by: dm/March 12, 2004

Initialed by: J.DuBeau 3/17/04

Final: March 19, 2004

Filename: N20164S58Lblrev.doc

RPM LABELING REVIEW

**This is a representation of an electronic record that was signed electronically and
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/s/

Diane V. Moore
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CSO

Julieann DuBeau
3/22/04 07:25:45 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-058

CORRESPONDENCE

Aventis Pharmaceuticals



November 14, 2003

Robert Justice, MD, Director
Food and Drug Administration
Central Document Room (HFD-180)
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

NDA 20-164 ———
Lovenox® (Enoxaparin Sodium Injection)
Response to FDA Request for Additional Information
RE: Deletion of One-Point Cut Ampule

Dear Dr. Justice:

Reference is made to the supplemental New Drug Application cited above for LOVENOX® (enoxaparin sodium) Injection and to our ——— letter to the Agency requesting withdrawal of Supplement —, without prejudice for future consideration, pursuant to 21 CFR §314.65. On September 23, 2003, in a telephone conversation between Ms. Dianne Moore (FDA) and Dr. Christine Chansky (Aventis), Ms. Moore confirmed that Aventis could proceed with deletion of the directions for use of the One Point Cut ampule, currently contained in the approved Lovenox® prescribing information.

As indicated on the attached Form FDA356H, this supplemental application provides for changes in the labeling section of the approved New Drug Application for LOVENOX®. With this letter, Aventis is providing the enclosed documentation to support deletion of the one point ampule from the **DESCRIPTION, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED** sections of the approved label for Lovenox®:

Proposed Labeling Text
Final Printed Package Insert
Summary

The revised labeling will be available on the Aventis intranet. in December 2003. It may not be available for use in all packages sold or distributed from the Company's manufacturing facilities until third quarter 2004.

This submission is formatted as required in Title 21 paragraph §314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Aventis Pharmaceuticals, is providing one Compact Disk (CD) which contains the submission. All of the information is contained on one CD and is not more than 100MB. Aventis certifies that we have taken precautions to ensure that all electronic media are free from computer viruses (Norton Anti-Virus 7.50.846, Scan Engine Version 4.1.0.6, Virus Definition File Version 51002h with an updated date of October 2, 2003).

A list of reviewers from the Division of Gastrointestinal and Coagulation Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Robert Justice, MD, Director, Division of Gastrointestinal and Coagulation Drug Products.

Aventis Pharmaceuticals considers the information contained in this submission private and confidential in accordance with provisions established in 21 CFR §312.130 and §314.430 and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis.

If you should have any questions or comments, please do not hesitate of contact me at 908- 304-6278 or, in my absence, Steve Caffé, MD at 908-231-5863.

Sincerely,



Christine Chansky, MD, JD
Director, Regulatory Liaison
Global Drug Regulatory Affairs

Attachment: CD

Desk Copy (letter only)

Robert Justice, M. D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-058

Aventis Pharmaceuticals, Inc.
Attention: Christine Chansky, M.D., J.D.
200 Crossing Blvd.
Bridgewater, NJ 08807

Dear Dr. Chansky:

We have received your supplemental drug 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-058

Date of supplement: November 14, 2003

Date of receipt: November 17, 2003

This supplemental application proposes the following changes: Deletion of the one point ampule from the **DESCRIPTION, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 16, 2004, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and research

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Attention: Document Room 8B-45

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, call me, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore

Regulatory Project Manager

Division of Gastrointestinal and Coagulation

Drug Products, HFD-180

Office of Drug Evaluation III

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Diane V. Moore

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