

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-039

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals Products, Inc.

Approval Date: October 24, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-039

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APPLICATION NUMBER:
NDA 20-164/S-039

APPROVAL LETTER

NDA 20-164/S-039

Aventis Pharmaceuticals Products Inc.
Attention: Ms. Janet K. DeLeon
1036 Marion Park Drive
P.O. Box 9627, H4-M2316
Kansas City, MO 64134-0627

Dear Ms. DeLeon:

Please refer to your supplemental new drug application dated May 25, 2000, received May 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

This "Changes Being Effectuated in 30 days" supplemental new drug application provides for the qualification of a new batch size _____ of Lovenox® 30 mg/0.3mL and 40mg/0.4mL pre-filled syringes on _____ of the manufacturing plant at Aventis Pharma Specialites, 180, rue Jean Jaures, 94700 Maisons-Alfort, France.

We have completed the review of this supplemental new drug 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.

If you have any questions, contact Karen Oliver, Project Manager, at (301) 827-7310.

Sincerely,

Liang Zhou, 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-039

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Zhou

HFD-180/J.Sieczkowski

HFD-095/DDMS-IMT

HFD-093/DDMS-IST

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: KO/October 24, 2000

final: KO/10/24/00/c:\data\mydocuments\NDA20164-S-039-10-24-00-AP-cbe.doc

(AP) APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-039

CHEMISTRY REVIEW

CHEMIST'S REVIEW # 1		1. <u>Organization:</u> HFD-180	2. <u>NDA number:</u> 20-164	
3. <u>Name and Address of Applicant (City & State):</u> Aventis Pharmaceuticals 10236 Marion Park Drive, P.O. Box 9627, Kansas City, MO 64134			4. <u>AF Number:</u>	
6. <u>Name of Drug:</u> Lovenox® Injection		7. <u>Nonproprietary Name:</u> enoxaparin sodium		5. <u>Supplement(s)</u> Numbers: SCS-039 Dates: 25 MAY 2000
8. <u>Supplement Provides for:</u> a new batch size _____ in the manufacture of Lovenox 30 mg/0.3 mL and 40 mg/0.4 mL on _____ of the manufacturing plant at Aventis Pharma Specialties, Maisons-Alfort, France.			9. <u>Amendments and Other (Reports, etc.) Dates:</u> SCS-026 SCS-027	
10. <u>Pharmacological Category:</u> Prevention of deep vein thrombosis		11. <u>How Dispensed:</u> RX XX OTC		12. <u>Related IND/NDA/DMF(s):</u>
13. <u>Dosage Form:</u> Injection (SVP)		14. <u>Potency:</u> 100 mg/mL		
15. <u>Chemical Name and Structure:</u> See Lovenox® Injection Package insert.			16. <u>Records and Reports:</u>	
			Current Yes <input checked="" type="checkbox"/> No	
			Reviewed Yes <input checked="" type="checkbox"/> No	
17. <u>Comments:</u> CBE-30. See Review Notes. cc: NDA 20-164 HFD-180/Div File HFD-181/CSO/K.Oliver HFD-180/L.Talarico HFD-180/J.Sieczkowski R/D init: L.Zhou AA\dob Draft 10-19-00 \F/T 10-23-00\WORD: n:\Wordfiles\chem\S\20164039.1JS				
18. <u>Conclusions and Recommendations:</u> The submitted supplemental information supports the proposed change to drug product manufacturing. It is recommended that the supplement be approved.				
19. <u>Reviewer</u>				
Name: Joseph Sieczkowski, Ph.D.		Signature		Date Completed: October 17, 2000

SUPPLEMENTAL INFORMATION:

The information submitted in this supplement is for a new batch size _____ for the manufacture of Lovenox® Injection (30 mg and 40 mg prefilled syringes) by _____ on manufacturing _____ approved) at Aventis Pharma Specialties, Maisons-Alfort, France site. The _____ batch was fully validated on 3 batches of 40 mg/0.4 mL prefilled syringes which were put on the approved stability protocol (Tab 4.24 Stability). No changes were made to the CMC of the drug substance or to the container closure system. The supplemental submission was submitted in accordance with "Guidance for Industry, Changes to the Approved NDA or ANDA (November 1999) under Section VII.C.1. (d).

The following information was submitted:

4.1 Introduction

4.2 Drug Product

4.2.1 Qualitative & Quantitative Composition

4.2.2 Manufacturer & Method of Manufacture

4.2.2.1 Manufacturing Report

4.2.2.2 Sterilization Process Validation Report

4.2.3 Specifications and Analytical Methods

4.2.4 Stability

4.2.4.1 Stability Data for Lots 4758, 4761, & 4764

4.2.4.2 Cross Reference Table – Active & Inactive Components

4.2.4.3 Certificates of Analysis

4.2.4.4 Stability Protocol and Commitment

4.3 Manufacturing Batch Records

4.3.1 Batch Record Translation Template

4.3.2 Translation Tables for Handwritten Comments

4.3.3 Batch Records for lots 4758, 4761, and 4764

NOTE: 4.3.3 appears in Volume 2.

COMMENT:

1. All the appropriate information has been submitted (see 4.2 – 4.3 above) to support the manufacturing change which is essentially an _____ drug product formulation.
2. Aventis Pharmaceuticals is very experienced in manufacturing the drug product and already manufactures different batch sizes on _____ at the Marion-Alfort, France site. Previously approved supplements are SCS-026, _____ batches (30 and 40 mg prefilled syringes) on _____ and SCS-027, _____ batches (30 and 40 mg

prefilled syringes) on ———. On the basis of the Aventis previous experience with the drug product, it was decided, in this Reviewers opinion, that a consult to Microbiology should not be sent.

3. Data (including stability) and CMC information submitted for batch number 4758 (40 mg/0.4 mL syringes), batch number 4761 (40 mg/0.4 mL syringe), and batch number 4764 (40 mg/0.4 mL syringe). See also Cross Reference Table for drug product batch number versus enoxaparin sodium batch numbers on page 120. The information submitted for the 40 mg/0.4 mL syringes is adequate to support the manufacture of the 30 mg/0.3 mL syringe.
4. The nine months of stability data for the three batches manufactured are satisfactory.
5. FDA CDER EES submitted for this supplement SCS-039 notes that the drug product manufacturing site is "Acceptable."

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-039

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

NDA 20-164/S-039

CBE-30 SUPPLEMENT

Aventis Pharmaceuticals Products Inc.
Attention: Janet K. DeLeon
10236 Marion Park Drive
P.O. Box 9627, H4-M2316
Kansas City, MO 64134-0627

Dear Ms. DeLeon:

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-039

Date of Supplement: May 25, 2000

Date of Receipt: May 26, 2000

This supplemental application, submitted as a "Supplement - Changes Being Effected in 30 days," proposes the following change: the qualifying a new batch size _____ of Lovenox® 30 mg/0.3mL and 40mg/0.4mL pre-filled syringes manufactured at the Aventis Pharma Specialites, 180, rue Jean Jaures, 94700 Maisons-Alfort, France, site.

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 July 25, 2000 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7457.

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-039

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Zhou

HFD-180/J.Sieczkowski

DISTRICT OFFICE

Drafted by: KO/June 8 2000

filename: KO/06/08/00/c:\data\mydocuments\NDA20164-S-039-06-08-00-cbe30.doc

CBE-30 SUPPLEMENT ACKNOWLEDGEMENT (AC)