CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals Products, Inc.

Approval Date: January 9, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Aventis Pharmaceuticals Products Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Global Drug Regulatory Affairs
Global Therapeutic Area Head
Route 202-206
PO Box 6800
Bridgewater, NJ 08807-0800

Dear Mr. Carrado:

Please refer to your supplemental new drug applications dated August 23, 2000, received August 24, 2000 [S-040], and August 14, 2001, received August 15, 2001 [S-045 and S-046], submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submissions dated October 27, and December 1 and 29, 2000, and July 11, August 14, November 12 and 28, 2001, to S-040.

These supplemental new drug applications provide for the following:

> Supplement 040, submitted as a "Supplement - Changes Being Effected" (CBE) supplement, provides for the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves"; and (2) in the PRECAUTIONS section, the "Pregnancy" subsection,, the "*Non-teratogenic Effects*" sub-subsection, the addition of a third paragraph in the sub-subsection describing a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to prevent thromboembolism.
>
> Supplement 045, submitted as a prior approval supplement, provides for revisions to the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection of the package insert, specifically updating the number of spinal epidural hematomas.
>
> Supplement 046, submitted as a prior approval supplement, provides for the revisions to the PRECAUTIONS section, the "Pregnancy" subsection of the package insert.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon final printed labeling (FPL) submitted August 14, 2001. Accordingly, these supplemental applications are approved effective on the date of this letter.

However, at the next printing, we request that you revise the Maison-Alfort PI as follows: in the ADVERSE REACTIONS section, the "Major bleeding Episodes Following Hip or Knee Replacement Surgery" table, information pertinent to that table should be the same column to facilitate continuity and ease of readability. As submitted, the table is located at the bottom of column 4 and at the top of column 5.

Submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We request that the letter (draft submitted November 28, 2001) communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care within 30 days of receipt of this letter. Further, please submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

Victor F. C. Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal and 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
1/9/02 10:51:18 AM
For Dr. Victor Raczkowski

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-040

Aventis Phamaceuticals Products Inc.
C/O Quintiles, Inc.
Attention: Ms. Michelle Kliewer
Post Office Box 9708
Kansas City, MO 64134-0708

Dear Ms. Kliewer:

Please refer to your supplemental new drug application dated August 23, 2000, received August 24, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submissions dated October 27, and December 1 and 18, 2000.

This "Changes Being Effected" supplemental new drug application proposes the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves", to read: "

(see PRECAUTIONS: Pregnancy)."; and (2) in the PRECAUTIONS section, the "Pregnancy" subsection, the addition of a third paragraph in the subsection, to read: "In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. In the PRECAUTIONS section, in the new subsection entitled "Prosthetic Heart Valves", revise the subsection to read as follows:

Prosthetic Heart Valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

2. In the PRECAUTIONS section, the "Pregnancy" subsection, the "*Non-teratogenic Effects*" sub-subsection, the second, stand-alone paragraph, in the sub-subsection should be revised to read as follows:

> In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to [redacted]

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Further, we recommend that you issue a "Dear Doctor" letter to inform physicians of the important safety information regarding the use of enoxaparin in patients with prosthetic heart valves, particularly in pregnant women. Please submit the draft "Dear Doctor" letter to the Agency for comment prior to issuance.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form,

not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Lilia Talarico
12/21/00 04:15:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

LABELING REVIEWS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-040

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Material Reviewed

Submission Date(s): August 23, 2000

Receipt Date(s): August 24, 2000

Background and Summary Description: Supplement 040, submitted as a "Supplement - Changes Being Effected" (CBE) supplement, provides for the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves", to read:

[redacted]

; and (2) in the PRECAUTIONS section, the "Pregnancy" subsection, the addition of a third paragraph in the subsection, to read: "In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

[redacted]

On December 18, 2000, the sponsor submitted revised final printed labeling (FPL), incorporating the labeling changes approved November 17, 2000 in S-036. Since the CBE supplement 040 provided for FPL in the original submission (08/23/00), the revised FPL submitted December 18, 2000, will be coded as a "Correspondence" and will not be reviewed as FPL for this supplement.

Review

PACKAGE INSERT

The final printed labeling (FPL) for the package inserts, submitted August 23, 2000, identified as "50057513 Rev. 7/00 508539E" (Maison Alfort) and "50057514 Rev. 7/00" (Dagenham), was compared to the package insert text enclosed in the November 17, 2000 approval letter for S-036. The submitted FPL does not incorporate the text approved in S-036. Therefore, only the labeling changes provided for in S-040 will be reviewed.

1. In the WARNINGS section, a new subsection titled "Prosthetic heart valves" was added to read:

Prosthetic heart valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

This additional information was reviewed by the Medical Officer, Dr. Min Lu (see Medical Officer's Review dated December 13, 2000) and it is UNACCEPTABLE. The subsection should be revised to read as follows:

Prosthetic Heart Valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

2. In the PRECAUTIONS section, the "Pregnancy" subsection, the "*Non-teratogenic Effects*" sub-subsection, the following information was added as the second, stand-alone paragraph, in the sub-subsection to read:

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to

[redacted]

This additional information was reviewed by the Medical Officer, Dr. Min Lu (see Medical Officer's Review dated December 13, 2000) and it is UNACCEPTABLE. The subsection should be revised to read as follows:

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to

[redacted]

Conclusions

1. The following changes are UNACCEPTABLE: 1. and 2.

2. An approvable letter should be issued.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

cc:
Original NDA 20-164/S-040
HFD-180/Div. Files
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/M.Lu
HFD-180/K.Oliver
R/D init: K.Robie-Suh 12/20/00
R/D init: L.Talarico 12/20/00
draft: KO/December 19, 2000
final: KO/12/21/00/c:\data\mydocuments\NDA20164-S-040-12-19-00-labrev

CSO REVIEW

/s/

Karen Oliver
12/21/00 03:02:59 PM
CSO

Lilia Talarico
12/21/00 04:14:14 PM
MEDICAL OFFICER

Division of Gastrointestinal & Coagulation Drug Products
CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-040, 045, and 046

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Material Reviewed

Submission Date(s): August 14, 2001

Receipt Date(s): August 15, 2001

Background and Summary Description

Supplement 040: Submitted August 23, 2000 as a "Supplement - Changes Being Effected" (CBE) supplement, provides for the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves", to read: "

[redacted]

(see PRECAUTIONS: Pregnancy)."; and
(2) in the PRECAUTIONS section, the "Pregnancy" subsection, the addition of a third paragraph in the subsection, to read: "In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

[redacted]

An approvable letter was issued on December 21, 2000.

Supplement 045: Submitted August 14, 2001 as a prior approval supplement, provides for the following: revisions to the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection of the package insert, specifically updating the number of spinal epidural hematomas.

Supplement 046: Submitted August 14, 2001 as a prior approval supplement, provides for the following: revisions to the PRECAUTIONS section, the "Pregnancy" subsection of the package insert.

The August 14, 2001 submission contains identical final printed labeling for S-040, 045, and 046. Therefore, a single review will identify the changes to the labeling, specific to each supplement.

Review

PACKAGE INSERT (PI)

The final printed labeling (FPL) for the package inserts, submitted August 14, 2001 identified as "50063316 Rev. 07/01" (Maison-Alfort) and "50063181 Rev. 07/01" (Dagenham), was compared to the currently approved package inserts, identified as "50063314 Rev. 05/01A" (Maison-Alfort) and "50062180 Rev. 05/01A" (Dagenham); the revisions requested in the December 12, 2000 approvable letter for S-040; the changes requested in the January 4, 2001 Agency letter to the PRECAUTIONS section, the "Pregnancy" subsection of the PI, and changes requested in the January 30, 2001 Agency letter to the PRECAUTIONS section, the "Ongoing Safety Surveillance" subsection of the PI. The FPL is identical except for the following:

1. The identification numbers have changed.

   These changes are ACCEPTABLE.

2. For both the Maison-Alfort and Dagenham PIs, the running heads at the top of each have been moved from the right edge of the column to the center of the column.

   This change is ACCEPTABLE.

3. For the Maison-Alfort PI, the bar code, name of the drug, and identification number positioned vertically in the margin to the left of the DESCRIPTION section (located near the top of column 1) has been re-positioned vertically in the margin to the left of the CLINCAL TRIALS section text (located near the bottom of column 1).

   This change is ACCEPTABLE.

4. For the Maison-Alfort PI, the ADVERSE REACTIONS section, the "Major Bleeding Episodes Following Hip or Knee Replacement Surgery" table (at the bottom of column 4), information pertinent to the table is separated from the table, as it is located at the top of column 5). The information at the top of column 5 includes the following:

   > NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox Injection patients versus 1.8% of the placebo patients.

This is UNACCEPTABLE. The sponsor should be requested to revise the PI at the next printing such that information related to a table is contained in a single column of text.

5. **Supplement 040** provides for changes in the WARNINGS section, the "Prosthetic Heart Valves" subsection as follows:

As requested in the December 21, 2001 approvable letter for S-040:

Again — this is "WARNINGS"

PRECAUTIONS section:

Prosthetic Heart Valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

Revised, as requested in the January 4, 2001 Agency letter, to read:

PRECAUTIONS section:

Prosthetic Heart Valves:

[redacted]

[(see **PRECAUTIONS: Pregnancy).**

Revised, as agreed upon in a March 2, 2001 facsimile, and submitted for Agency review on July 11, 2001, to read:

WARNINGS section:

Prosthetic Heart Valves: The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism **(see PRECAUTIONS: Pregnancy).**

These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.

6. **Supplement 040** provides for changes in the PRECAUTIONS section, the "Pregnancy" subsection, the "*Non-teratogenic Effects*" sub-subsection. The second, stand-alone paragraph, in the sub-subsection has been changed:

As requested in the December 21, 2001 approvable letter for S-040:

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to

[ ]

Revised, as requested in the January 4, 2001 Agency letter, and agreed upon in a March 2, 2001 facsimile, to read:

> In a clinical study of pregnant women with prosthetic valves given enoxaparin (1mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are ——— reports of ——— ———prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events
>
> [ ]

Submitted July 11, 2001 and re-submitted August 14, 2001, to read:

> In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves).**

These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.

7. **Supplement 045** provides for changes in the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection. The number of reports of epidural or spinal hematoma has been revised

from:

> Since 1993, there have been ———— reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture.

Did not locate previous any labeling citing more than 79"

to:

> Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture.

This change, as requested by the Agency based on the current number of epidural or spinal hematoma events, is ACCEPTABLE.

8. **Supplement 046** provides for changes to the PRECAUTIONS section, the "Pregnancy" subsection, the *Teratogenic Effects* sub-subsection, a second paragraph was added:

> As requested in the January 4, 2001 Agency letter and agreed upon in the March 2, 2001 facsimile, to read:
>
> > There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy [redacted] cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established.
>
> Submitted July 11, 2001 and re-submitted August 14, 2001, to read:
>
> > There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.
>
> **These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.**

9. **Supplement 046** provides for changes to the PRECAUTIONS section, the "Pregnancy" subsection, the *Non-Teratogenic Effects* sub-subsection, a first paragraph was added:

As requested in the January 4, 2001 Agency letter

There have been [redacted] of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Submitted July 11, 2001, and re-submitted August 14, 2001, to read:

There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.

10. At the end of the package insert, the prescribing information date has been updated to July 2001.

This change is ACCEPTABLE.

Conclusions

The identified changes are ACCEPTABLE. The sponsor should be requested to revise the PI, as the next printing, as identified in 4. above.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Victor F. C. Raczkowski, M.D.,
Division Director

cc:
Original NDA 20-164/S-040, 045, 046
R/D init: K.Robie-Suh 01/03/02
R/D init: J.Korvick 01/07/02
draft: KO/October 3, 2001
final: KO/01/08/02/c:\data\mydocuments\NDA20164-S-040-045-046-10-02-01-labrev

CSO REVIEW

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

/s/

Karen Oliver
1/8/02 12:15:09 PM
CSO

Joyce Korvick
1/9/02 10:49:07 AM
MEDICAL OFFICER
for Dr. Victor Raczkowski

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

MEDICAL REVIEWS

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-164 (SLR-040, BM)
Sponsor:	Aventis Pharmaceuticals Products Inc.
Drug name:	Lovenox® (enoxaparin sodium) Injection
Submission:	Labeling Supplement
Date submitted:	August 23, 2000; October 27, 2000; December 4, 2000
Review completed:	December 8, 2000
Medical reviewer:	Min Lu, M.D., M.P.H.

1. Introduction and Background
The sponsor has submitted a supplement for labeling change as "Changes Being Effected" to include safety information for pregnant women with prosthetic heart valves in Warnings and Precautions sections as follows.

1). Warnings section

The sponsor proposes to add a new section under Warnings that reads:

"Prosthetic heart valves:

[

(see Precautions: Pregnancy)".

]

2). Precautions section

The sponsor propose to add the following paragraph at the end of Pregnancy section under Precautions:

"In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

[

]

2. Material reviewed
NDA 20-164 SLR-040 –Summary, submitted August 23, 2000
NDA 20-164 SLR-040 BM, Volume 160.1-160.4, Study ENO-ZA-301 study and case report forms, submitted October 27, 2000.

3. Enoxaparin and its use in patients with prosthetic heart valves

Use of enoxaparin for thromboembolism prophylaxis in patients with prosthetic heart valves is not approved as an indication in current labeling. Patients with artificial heart valves, when undergoing non-cardiac surgery or upon becoming pregnant, are often switched from oral anticoagulation to intravenous or subcutaneous unfractionated heparin. Recently, ten cases of obstruction of prosthetic valves, secondary to thrombosis, were reported internationally when patients were receiving enoxaparin subcutaneous injection for thromboembolism prophylaxis. These patients included seven pregnant women. There were no reports in the United States. Since enoxaparin is not indicated in patients with prosthetic heart valves in United States, it is difficult to estimate the use of enoxaparin in this situation.

1) The Sponsor's Safety Database Search
The sponsor's safety database search for reports regarding enoxaparin and prosthetic heart valve obstruction/failure from first launch of enoxaparin in 1986 to March 13, 2000

have identified 10 cases. The database search was based on prosthesis and artificial heart valves (reporter term). Among the 10 cases, 2 were reported from South Africa and 8 were reported from Israel. Two Israeli cases had been published in "The Annals of Thoracic Surgery". The remaining 6 Israeli cases were reported by a solitary physician. The sponsor reported that 3 of these reports had been communicated to this physician by a cardiac surgeon. The following table summarizes the available information for the 10 cases.

Summary of ten cases with prosthetic heart valve thrombosis

Case #	Sources	Patients	Enoxaparin received	Adverse reactions	Outcomes
IL01-00100 Israel	Reported by physician	Pregnant woman, unknown age	20 mg daily, unknown duration	Prosthetic mitral valve thrombosis	death
IL01-00101 Israel	Reported by physician	Woman, unknown age	40mg bid, unknown duration	Aortic prosthetic valves clotted	Surgical repair
IL01-00102 Israel **3 cases**	Reported by physician	Pregnant women, Unknown age	40 mg daily, unknown duration	Prosthetic heart valve clotted	Surgical repair
IL01-00110 Israel	Reported by physician	Woman, Unknown age	40 mg daily, unknown duration	"stuck" heart valves	Surgical repair
IL01-00103 Israel	Literature report	72 year man	40 mg bid for 37 weeks	Aortic prosthetic valve thrombosis	Urgent aortic valve replacement
IL01-00104 Israel	Literature report	29 year pregnant woman	40 mg daily for 32 weeks	Prosthetic mitral valve thrombosis	Mitrial valve replacement
ZA01-00209 South Africa	Study ENO-ZA-301	32 year pregnant woman	80 mg bid for 37 days	Prosthetic mitral valve thrombosis	Death and death of the fetus
ZA01-00210 South Africa	Study ENO-ZA-301	36 year pregnant woman	80 mg bid for 35 days	Aortic prosthetic valves clotted	Death and death of the fetus

Reviewer's table

Among the ten cases, there were 3 deaths caused by prosthetic valve thrombosis in pregnant women with deaths of fetus. Remaining 7 patients required surgical repair. Seven of 10 cases were pregnant women with prosthetic valves. Others were 2 women with unknown age and one 72-year-old man. Enoxaparin dosage varied from 20 mg daily to 80 mg (1 mg/kg) twice a day. The duration of enoxaparin use was up to 37 days.

2) Clinical Studies in Patients with Artificial Heart Valves

Some enoxaparin studies have been carried out or are presently in progress in patients with prosthetic heart valves.

Study ENO-ZA-301 (HIPCAT Study):
The study ENO-ZA-301 was a multi-center, open, randomized, controlled trial to assess the maternal and fetal safety and efficacy of high dose enoxaparin for the anticoagulation of pregnant patients with prosthetic heart valves, in comparison to standard therapy (warfarin/unfractionated heparin). This study was carried out in South Africa and was scheduled to enroll 110 pregnant women. The patients in this study were all treated with either enoxaparin 1 mg/kg bid sc or warfarin/heparin, beginning at the time of pregnancy diagnosis. The study was terminated after only 11 patients had been enrolled (7 into the enoxaparin group and 4 into the control group) because two deaths due to prosthetic valve thrombosis occurred in enoxaparin-treated patients. These cases were considered therapeutic failure. The safety board requested that the study be terminated. The two cases are summarized above (ZA01-00209 and ZA01-00210). The narratives of the two cases are attached in Appendix 1.

In this study, other reported adverse events included one case of severe hemorrhage that occurred in an enoxaparin-treated patient 8 days postpartum and was caused by retained placenta fragments, one case of vaginal bleeding with incomplete miscarriage at 12-weeks in warfarin/unfractionated heparin-treated patients, and one case of intrauterine death at 19-weeks in warfarin-treated patients.

Grant-in-Aid study
A Grant-in-Aid study is presently being carried out in the United States by Dr. ———— ————, M.D., et. al., Division of Cardiovascular Diseases and Internal Medicine, ———— ———————— (IND ————). The protocol is to explore the use of [redacted] The investigator was informed of the two fatalities having occurred in pregnant patients in the ENO-ZA-301 study and the reports from Israel. The study has been put on hold until IRB review.

Argentina study
A clinical study is presently in progress in Argentina to evaluate efficacy and safety of enoxaparin in patients with either mechanical valvular prosthesis, or chronic atrial fibrillation, or with rheumatic mitral stenosis, or previous embolism, or presence of thrombus in left atrium, who undergo surgical procedures requiring that oral anticoagulation be stopped. A total of 15 patients have been enrolled. The number of enrolled patients with mechanical valvular prosthesis is not provided by the sponsor. The dose of enoxaparin is 1 mg/kg bid, to be administered perioperatively. The total number of patients scheduled is 200 with 3 centers participating. Until now, no case of thrombosis of prosthetic heart has been reported. The investigators have been informed of the reports from South Africa and Israel.

3) Literature Reports
Two cases of thrombosed mechanical heart valves in pregnant women having received enoxaparin were published in Annals of Thoracic Surgery 2000; 69(1): 264-6 by Lev-Ran et. al. These two cases have been summarized above. No additional report was identified from Medline search by this reviewer at the present time.

4) Adverse Event Reporting System (AERS) Search
No additional cases of prosthetic valve thrombosis have been identified from the search of the FDA AERS database conducted by this reviewer on 11/22/2000.

4. Conclusions and Recommendations
The sponsor has submitted a supplement for labeling changes as "change being effected" to include safety information in warnings and precautions for pregnant women with prosthetic valve.

A total of 10 cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic heart valves who had received enoxaparin for thrombosis prophylaxis from post-marketing spontaneous report system. Seven of these cases were pregnant women and 3 of them died due to prosthetic heart valve thrombosis, which led to deaths of fetus.

Two deaths of pregnant women were reported in 7 enoxaparin-treated patients in a clinical trial (ENO-ZA-301) in South Africa. This trial was terminated after only 11 patients had been enrolled into the study because of the two deaths. The remaining 8 cases of prosthetic valve thrombosis including one death of a pregnant woman were reported from Israel.

Enoxaparin dosage that was used in seven pregnant women with prosthetic heart valves ranged from 20mg daily to 80 mg (1mg/kg) twice a day. The duration of treatment was up to 37 days. The sponsor considered these cases as treatment failure. The reasons for therapy failure were not clear.

There has been no adequate and well-controlled study for enoxaparin use in pregnant women with prosthetic heart valves. The indication for enoxaparin use in pregnant women with prosthetic heart valves is not approved in the current labeling.

Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism. Important safety information for enoxaparin use in pregnant women with prosthetic heart valves should be included in the U.S. labeling.

This reviewer has the following recommendations:
1. The request to add safety information for pregnant women with prosthetic heart valves in Warnings and Precautions sections should be approved with labeling recommendation (See attached Appendix 1).
2. All seven cases of prosthetic valve thrombosis including 3 deaths and 4 requiring surgical repair in pregnant women should be described in precautions section in the labeling (See attached Appendix 1).

3. The sponsor should provide a "Dear Doctor" letter to inform physicians the important safety information for enoxaparin use in pregnant women with prosthetic heart valves.

Min Lu, M.D., M.P.H.

cc:
NDA 20-164/SLR-040
HFD-180/Division file
HFD-180/L Talarico
HFD-180/K Robie-Suh
HFD-180/M Lu
HFD-180/K Oliver
HFD-180/J Choudary
HFD-720/T Permutt
HFD-180/L Zhou
HFD-180 S Doddapaneni

12/8/2000

Appendix 1. Labeling comments

1). Warnings section

"Prosthetic heart valves:

[redacted]

(see Precautions: Pregnancy)".

2). Precautions section

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Appendix 2. The Narratives of the Two Deaths in Study ENO-ZA-301

Case #ZA01-00209

An investigator reported a 32 year old pregnant woman developed thrombosis of her prosthetic mitral valve and died on ———. The mother's death subsequently led to the death of the fetus. The patient presented to the hospital on ——— complaining of hematemesis, dyspnea, and orthopnea. She was treated with diuretics, and transferred to another hospital where she was diagnosed with restricted notion of the prosthetic valve. She developed cardiogenic shock and became acidotic. She was transferred to a third hospital for emergency valve replacement, but died before the operation could be performed. Her medical history was significant for rheumatic heart disease with prosthetic mitral valve (carbo medics size 3]) placement on ———. The patient was approximately 12 weeks pregnant at the time of her death. Enoxaparin (80 mg subcutaneouly twice daily) was administered from ——— to ——— for prosthetic valve thrombosis prophylaxis. Tissue plasminogen activator complex was given at the third itospita1, in an attempt to improve her condition. Her anti-Xa levels on 18-Oct-99 at 1100 and 1400 hours were 0.33 and 0.78 IU/ml, respectively. Examination on admission to the second hospital revealed florid pulmonary edema with extensive crackles in the chest. Valve clicks were not audible. Echocardiography revealed very restricted motion of the valve disc and a mean gradient across the mitral valve prosthesis of approximately 20 mm Hg. Transesophageal Echo performed at the third institution revealed an extensive thrombus around the valve ring with prolapse into and obstruction of the valve orifice in diastole. Her ejection fraction was 52%. Examinations of the fetus early in pregnancy did not reveal any abnormality. The investigator considered the events as probably related to inadequate coagulation afforded by enoxaparin. No autopsy was performed.

Case #ZA01-00210

An investigator reported a 36 year-old pregnant woman developed cardiogenic shock and a clotted aortic prosthetic valve. These events subsequently led to her death, as well as the death of the fetus. During the evening of ——— the patient awoke with severe dyspnea. She was brought to the hospital, where she was diagnosed with cardiogenic shock secondary to aortic valve dysfunction. She died approximately one hour after admission. Her medical history was significant for a prosthetic mitral valve (23 hall kaster) ——— due to mitral stenosis, and a prosthetic aortic valve (27 hall kaster) ——— secondary to mixed aortic valve disease. She had two miscarriages previously while receiving warfarin. The patient was 31 weeks pregnant at the time of her death. Enoxaparin (80 mg twice daily) was administered from 2-Aug-99 to 6-Nov-99 for prosthetic valve thrombosis prophylaxis. Her anti-Xa level on 18-Oct-99 was 0.43 IU/ml. Examination on admission revealed sinus tachycardia, loud systolic and early diastolic murmur and the lack of audible aortic valve clicks. Post-mortem examination was significant for biventricular cardiomegaly, associated with prosthetic replacement of aortic and mitral valve. Fibrin thrombi on the inferior aspect of both aortic and mitral rings were noted. Inflammatory cells and microorganisms were absent. Chronic rheumatic tricuspid valve disease with stenosis and incompetence was demonstrated, as well as obliterative pericarditis related to previous cardiac surgery. Hepatosplenomegaly, mild pulmonary congestion, edema and minimal pleural effusion was also fond. Post-mortem examinations also revealed a normal fetus, with the umbilical cord loosely looped twice around the neck. The investigator considered the events as probably related to enoxaparin therapy.

/s/

Min Lu
12/13/00 09:46:38 AM
MEDICAL OFFICER

Kathy Robie-Suh
12/13/00 12:21:21 PM
MEDICAL OFFICER

Lilia Talarico
12/13/00 07:15:28 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS MEDICAL OFFICER'S REVIEW

NDA: 20-164/SLR-040-AF

Sponsor: Aventis Pharmaceuticals Products Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Drug name: **Lovenox** (enoxaparin sodium)

Route of Administration: Subcutaneous Injection

Subject: Submission of Final Printed Labeling and a Draft "Dear Doctor" Letter

Date submitted: August 14, 2001

Date received: August 15, 2001

Date assigned: October 3, 2001

Review completed: November 1, 2001

Reviewer: Ruyi He, M.D.

1 BACKGROUND:

In this submission, the sponsor submitted the final printed labeling and a draft "Dear Doctor" letter, after multiple communications with the sponsor as following:

- December 21, 2000 Agency approvable letter for S-040 (Prosthetic Heart Valve)
- January 4, 2001 Agency request letter for changes in labeling (Pregnancy/congenital)
- January 30, 2001 Agency request letter for changes in labeling (Ongoing Safety Surveillance)
- March 2, 2001 Agency revised draft labeling (fax)
- June 19, 2001 Agency approvable letter for FPL for S-020, 030, 034, 036, and 037
- July 11, 2001 Aventis Response to Request: Proposed Labeling for S-040, Pregnancy/congenital, and Ongoing Safety Surveillance.

The revised labeling is acceptable. In this review, I will provide my comments and recommendations for the "Dear Doctor" letter.