

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-138

20-164 S-075

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lovenox safely and effectively. See full prescribing information for Lovenox.

Lovenox® (enoxaparin sodium injection) for subcutaneous and intravenous use
Initial U.S. Approval: 1993

WARNING: SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning.

- Enoxaparin use in patients undergoing spinal/epidural anesthesia or spinal puncture increases the risk of spinal or epidural hematoma, which may cause long-term or permanent paralysis (5.5)
- Risk is increased by:
 - Indwelling epidural catheters for analgesia (5.5)
 - Drugs affecting hemostasis [e.g., nonsteroidal anti-inflammatory drugs, platelet inhibitors, anticoagulants] (5.5, 7)
 - Traumatic or repeated spinal or epidural puncture (5.5)

-----RECENT MAJOR CHANGES-----

Indications and Usage (1.4), 5/2007
Dosage and Administration (2) 5/2007
ST-segment Elevation Myocardial Infarction
Warnings and Precautions (5.2) 5/2007
Percutaneous coronary revascularization procedures

-----INDICATIONS AND USAGE-----

Lovenox is a low molecular weight heparin [LMWH] indicated for:

- Prophylaxis of deep vein thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness (1.1)
- Inpatient treatment of acute DVT with or without pulmonary embolism (1.2)
- Outpatient treatment of acute DVT without pulmonary embolism (1.2)
- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction [MI] (1.3)
- Treatment of acute ST-segment elevation myocardial infarction [STEMI] managed medically or with subsequent percutaneous coronary intervention [PCI] (1.4)

-----DOSAGE AND ADMINISTRATION-----

Indication	Standard Regimen (2.1, 2.3)	Severe Renal Impairment (2.2)
DVT prophylaxis in abdominal surgery	40 mg SC once daily	30 mg SC once daily
DVT prophylaxis in knee replacement surgery	30 mg SC every 12 hours	30 mg SC once daily
DVT prophylaxis in hip replacement surgery	30 mg SC every 12 hours or 40 mg SC once daily	30 mg SC once daily
DVT prophylaxis in medical patients	40 mg SC once daily	30 mg SC once daily
Inpatient treatment of acute DVT with or without pulmonary embolism	1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily (with warfarin)	1 mg/kg SC once daily

Outpatient treatment of acute DVT without pulmonary embolism	1 mg/kg SC every 12 hours (with warfarin)	1 mg/kg SC once daily
Unstable angina and non-Q-wave MI	1 mg/kg SC every 12 hours (with aspirin)	1 mg/kg SC once daily
Acute STEMI in patients <75 years of age [For dosing in subsequent PCI, see Dosage and Administration (2.1)]	30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC every 12 hours with aspirin)	30-mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC once daily
Acute STEMI in patients ≥75 years of age	0.75 mg/kg SC every 12 hours (no bolus)	1 mg/kg SC once daily (no bolus)

Do not use as intramuscular injection.
For subcutaneous use, do not mix with other injections or infusions.

-----DOSAGE FORMS AND STRENGTHS-----

- 100 mg/mL concentration (3.1):
- Prefilled syringes: 30 mg/0.3 mL, 40 mg/0.4 mL
 - Graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL
 - Multiple-dose vial: 300 mg/3 mL
- 150 mg/mL concentration (3.2):
- Graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL

-----CONTRAINDICATIONS-----

- Active major bleeding (4.1)
- Thrombocytopenia with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium (4.2)
- Hypersensitivity to enoxaparin sodium (4.3)
- Hypersensitivity to heparin or pork products (4.4)

-----WARNINGS AND PRECAUTIONS-----

- Use caution in conditions with increased risk of hemorrhage (5.1)
- Obtain hemostasis at the puncture site before sheath removal after percutaneous coronary revascularisation (5.2)
- Use caution with concomitant medical conditions (5.3)
- Use caution in case of history of heparin-induced thrombocytopenia (5.4)
- Monitor thrombocytopenia of any degree closely (5.5)
- Do not exchange with heparin or other LMWHs (5.6)
- Pregnant women with mechanical prosthetic heart valves not adequately studied (5.7)
- Multiple-dose formulations contain benzyl alcohol (5.8)
- Periodic blood counts recommended (5.9)

-----ADVERSE REACTIONS-----

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, and nausea

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

Discontinue agents which may enhance hemorrhage risk prior to initiation of Lovenox or conduct close clinical and laboratory monitoring (5.9, 7).

-----**USE IN SPECIFIC POPULATIONS**-----

- Severe renal impairment: Adjust dose for patients with creatinine clearance <30 mL/min (2.2)
- Hepatic Impairment (8.8)
- Low-weight patients: Observe for signs of bleeding (8.9)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [m/year]

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1 FULL PRESCRIBING INFORMATION
2

3 **WARNING: SPINAL / EPIDURAL HEMATOMAS**

4 When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed,
5 patients anticoagulated or scheduled to be anticoagulated with low molecular weight
6 heparins or heparinoids for prevention of thromboembolic complications are at risk of
7 developing an epidural or spinal hematoma which can result in long-term or permanent
8 paralysis.

9
10 The risk of these events is increased by the use of indwelling epidural catheters for
11 administration of analgesia or by the concomitant use of drugs affecting hemostasis such as
12 non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other
13 anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or
14 spinal puncture.

15
16 Monitor patients for signs and symptoms of neurological impairment. If neurologic
17 compromise is noted, urgent treatment is necessary.

18
19 Consider the potential benefit versus risk before neuraxial intervention in patients
20 anticoagulated or to be anticoagulated for thromboprophylaxis [see *Warnings and*
21 *Precautions (5.1) and Drug Interactions (7)*].

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23 **1 INDICATIONS AND USAGE**

24 **1.1 Prophylaxis of deep vein thrombosis**

25 Lovenox is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary
26 embolism:

- 27
- in patients undergoing abdominal surgery who are at risk for thromboembolic complications [see Clinical Trials Experience 14.1].
 - in patients undergoing hip replacement surgery, during and following hospitalization.
 - in patients undergoing knee replacement surgery.
 - in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

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33 **1.2 Treatment of Acute Deep Vein Thrombosis**

34 Lovenox is indicated for:

- 35
- the **inpatient treatment** of acute deep vein thrombosis **with or without pulmonary embolism**, when administered in conjunction with warfarin sodium;
 - the **outpatient treatment** of acute deep vein thrombosis **without pulmonary embolism** when administered in conjunction with warfarin sodium.

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40 **1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-wave**
41 **Myocardial Infarction**

42 Lovenox is indicated for the prophylaxis of ischemic complications of unstable angina and non-
43 Q-wave myocardial infarction, when concurrently administered with aspirin.

44

45 **1.4 Treatment of acute ST- segment Elevation Myocardial Infarction (STEMI)**

46 Lovenox has been shown to reduce the rate of the combined endpoint of recurrent myocardial
47 infarction or death in patients with acute STEMI receiving thrombolysis and being managed
48 medically or with Percutaneous Coronary Intervention (PCI).

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52 **2 DOSAGE AND ADMINISTRATION**

53 All patients should be evaluated for a bleeding disorder before administration of Lovenox, unless
54 the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring
55 Lovenox activity, routine monitoring of coagulation parameters is not required [see *Warnings*
56 *and Precautions (5.9)*].

57

58 For subcutaneous use, Lovenox should not be mixed with other injections or infusions. For
59 intravenous use (*i.e.*, for treatment of acute STEMI), Lovenox can be mixed with normal saline
60 solution (0.9%) or 5% dextrose in water.

61

62 Lovenox is not intended for intramuscular administration.

63

64 **2.1 Adult Dosage**

65 Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for
66 thromboembolic complications, the recommended dose of Lovenox is **40 mg once a day**
67 administered by SC injection with the initial dose given 2 hours prior to surgery. The usual
68 duration of administration is 7 to 10 days; up to 12 days administration has been administered in
69 clinical trials.

70

71 Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the
72 recommended dose of Lovenox is **30 mg every 12 hours** administered by SC injection.
73 Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours
74 after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12
75 (± 3) hours prior to surgery, may be considered. Following the initial phase of
76 thromboprophylaxis in hip replacement surgery patients, it is recommended that continued
77 prophylaxis with Lovenox 40 mg once a day is administered by SC injection for 3 weeks. The
78 usual duration of administration is 7 to 10 days; up to 14 days administration has been
79 administered in clinical trials.

80

81 Medical Patients During Acute Illness: In medical patients at risk for thromboembolic
82 complications due to severely restricted mobility during acute illness, the recommended dose of
83 Lovenox is **40 mg once a day** administered by SC injection. The usual duration of
84 administration is 6 to 11 days; up to 14 days of Lovenox has been administered in the controlled
85 clinical trial.

86

87 Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient**
88 **treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be

89 treated at home, the recommended dose of Lovenox is **1 mg/kg every 12 hours** administered
90 SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with
91 pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism
92 (who are not candidates for outpatient treatment), the recommended dose of Lovenox is **1 mg/kg**
93 **every 12 hours** administered SC or **1.5 mg/kg once a day** administered SC at the same time
94 every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should
95 be initiated when appropriate (usually within 72 hours of Lovenox). Lovenox should be
96 continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been
97 achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration
98 is 7 days; up to 17 days of Lovenox administration has been administered in controlled clinical
99 trials.

100
101 Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or
102 non-Q-wave myocardial infarction, the recommended dose of Lovenox is **1 mg/kg** administered
103 SC **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily).
104 Treatment with Lovenox should be prescribed for a minimum of 2 days and continued until
105 clinical stabilization. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox
106 has been administered in clinical trials. [See *Warnings and Precautions (5.2) and Clinical Trials*
107 *Experience (14.5)*].

108
109 Treatment of acute ST-segment Elevation Myocardial Infarction: In patients with acute ST-
110 segment Elevation Myocardial Infarction, the recommended dose of Lovenox is a **single IV**
111 **bolus of 30 mg** plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours
112 (maximum 100 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining
113 doses). Dosage adjustments are recommended in patients ≥ 75 years of age [see *Dosage and*
114 *Administration (2.3)*].

115
116 When administered in conjunction with a thrombolytic (fibrin-specific or non-fibrin specific),
117 Lovenox should be given between 15 minutes before and 30 minutes after the start of fibrinolytic
118 therapy. All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as
119 having STEMI and maintained with 75 to 325 mg once daily unless contraindicated. In the
120 pivotal clinical study, the Lovenox treatment duration was 8 days or until hospital discharge,
121 whichever came first. An optimal duration of treatment is not known, but it is likely to be longer
122 than 8 days.

123
124 For patients managed with Percutaneous Coronary Intervention (PCI): If the last Lovenox SC
125 administration was given less than 8 hours before balloon inflation, no additional dosing is
126 needed. If the last Lovenox SC administration was given more than 8 hours before balloon
127 inflation, an IV bolus of 0.3 mg/kg of Lovenox should be administered [see *Warnings and*
128 *Precautions (5.2)*].

129 **2.2 Renal Impairment**

130 Although no dose adjustment is recommended in patients with moderate (creatinine clearance
131 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients
132 should be observed carefully for signs and symptoms of bleeding.

133 The recommended prophylaxis and treatment dosage regimens for patients with severe renal
 134 impairment (creatinine clearance <30 mL/min) are described in Table 1 [see Use in Specific
 135 Populations (8.6) and Clinical Pharmacology (12.3)].
 136
 137

Table 1
Dosage Regimens for Patients with Severe Renal Impairment
(creatinine clearance <30mL/minute)

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Treatment of acute ST-segment Elevation Myocardial Infarction in patients <75 years of age	30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC once daily.
Treatment of acute ST-segment Elevation Myocardial Infarction in geriatric patients ≥75 years of age	1 mg/kg administered SC once daily (no initial bolus)

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140 **2.3 Geriatric patients with acute ST-Elevation Myocardial Infarction**

141 For treatment of acute ST-segment Elevation Myocardial Infarction in geriatric patients ≥75
 142 years of age, **do not use an initial IV bolus**. Initiate dosing with **0.75 mg/kg SC every 12**
 143 **hours (maximum 75 mg for the first two doses only, followed by 0.75 mg/kg dosing for the**
 144 **remaining doses)**[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)].
 145

146 No dose adjustment is necessary for other indications in geriatric patients unless kidney function
 147 is impaired [see Dosage and Administration (2.2)].
 148

149 **2.4 Administration**

150 Lovenox is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug
 151 products, should be inspected visually for particulate matter and discoloration prior to
 152 administration.
 153

154 The use of a tuberculin syringe or equivalent is recommended when using Lovenox multiple-
 155 dose vials to assure withdrawal of the appropriate volume of drug.

156

157

Lovenox must not be administered by intramuscular injection. Lovenox is intended for use under the guidance of a physician.

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For subcutaneous administration, patients may self-inject only if their physicians determine that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

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Subcutaneous Injection Technique: Patients should be lying down and Lovenox administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.

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Lovenox prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

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1. Remove the needle shield by pulling it straight off the syringe (see Figure A). If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

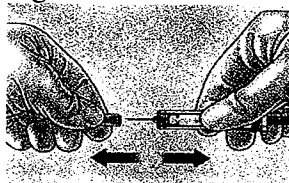
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Figure A



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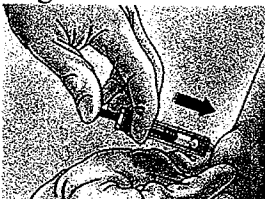
2. Inject using standard technique, pushing the plunger to the bottom of the syringe (see Figure B).

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Figure B



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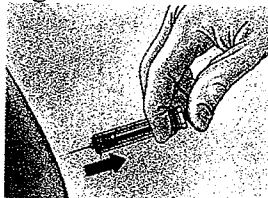
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3. Remove the syringe from the injection site keeping your finger on the plunger rod (see Figure C).

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Figure C



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4. Orient the needle away from you and others, and activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation (see Figure D).

Figure D



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5. Immediately dispose of the syringe in the nearest sharps container (see Figure E).

Figure E



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NOTE:

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- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient’s skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.

Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

Intravenous (Bolus) Injection Technique: For intravenous injection, the multiple-dose vial should be used. Lovenox should be administered through an intravenous line. Lovenox should not be mixed or co-administered with other medications. To avoid the possible mixture of Lovenox with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of Lovenox to clear the port of drug. Lovenox may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

222

223 3 DOSAGE FORMS AND STRENGTHS

224 Lovenox is available in two concentrations:

225

226 3.1 100 mg per mL

227 -Prefilled Syringes 30 mg / 0.3 mL, 40 mg / 0.4 mL

228 -Graduated Prefilled Syringes 60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / 1 mL

229 -Multiple-Dose Vials 300 mg / 3 mL

230

231 3.2 150 mg per mL

232 -Graduated Prefilled Syringes 120 mg / 0.8 mL, 150 mg / 1 mL

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234

235 4 CONTRAINDICATIONS

236 • Active major bleeding.

237 • Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the
238 presence of enoxaparin sodium.

239 • Known hypersensitivity to enoxaparin sodium (*e.g.*, pruritus, urticaria, anaphylactoid
240 reactions) [*see Adverse Reactions (6.2)*].

241 • Known hypersensitivity to heparin or pork products.

242 • Known hypersensitivity to benzyl alcohol (which is in only the multi-dose formulation of
243 Lovenox).

244

245 5 WARNINGS AND PRECAUTIONS

246 5.1 Increased Risk of Hemorrhage

247 Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox
248 and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis.
249 The risk of these events is higher with the use of post-operative indwelling epidural catheters or
250 by the concomitant use of additional drugs affecting hemostasis such as NSAIDs [*see boxed*
251 *Warning, Adverse Reactions (6.2) and Drug Interactions (7)*].

252

253 Lovenox should be used with extreme caution in conditions with increased risk of hemorrhage,
254 such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and
255 angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or
256 ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

257

258 Major hemorrhages including retroperitoneal and intracranial bleeding have been reported.
259 Some of these cases have been fatal.

260

261 Bleeding can occur at any site during therapy with Lovenox. An unexplained fall in hematocrit
262 or blood pressure should lead to a search for a bleeding site.

263

264 5.2 Percutaneous coronary revascularization procedures

265 To minimize the risk of bleeding following the vascular instrumentation during the treatment of
266 unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial

267 infarction, adhere precisely to the intervals recommended between Lovenox doses. It is
268 important to achieve hemostasis at the puncture site after PCI. In case a closure device is used,
269 the sheath can be removed immediately. If a manual compression method is used, sheath should
270 be removed 6 hours after the last IV/SC Lovenox. If the treatment with enoxaparin sodium is to
271 be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath
272 removal. The site of the procedure should be observed for signs of bleeding or hematoma
273 formation [see *Dosage and Administration (2.1)*].
274

275 **5.3 Use of Lovenox with Concomitant Medical Conditions**

276 Lovenox should be used with care in patients with a bleeding diathesis, uncontrolled arterial
277 hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and
278 hemorrhage.

280 **5.4 History of Heparin-induced Thrombocytopenia**

281 Lovenox should be used with extreme caution in patients with a history of heparin-induced
282 thrombocytopenia.

284 **5.5 Thrombocytopenia**

285 Thrombocytopenia can occur with the administration of Lovenox.

286
287 Moderate thrombocytopenia (platelet counts between $100,000/\text{mm}^3$ and $50,000/\text{mm}^3$) occurred at
288 a rate of 1.3% in patients given Lovenox, 1.2% in patients given heparin, and 0.7% in patients
289 given placebo in clinical trials.

290
291 Platelet counts less than $50,000/\text{mm}^3$ occurred at a rate of 0.1% in patients given Lovenox, in
292 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

293
294 Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below
295 $100,000/\text{mm}^3$, Lovenox should be discontinued. Cases of heparin-induced thrombocytopenia
296 with thrombosis have also been observed in clinical practice. Some of these cases were
297 complicated by organ infarction, limb ischemia, or death [see *Warnings and Precautions (5.4)*].
298

299 **5.6 Interchangeability with Other Heparins**

300 Lovenox cannot be used interchangeably (unit for unit) with heparin or other low molecular
301 weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa
302 and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for
303 use.
304

305 **5.7 Pregnant Women with Mechanical Prosthetic Heart Valves**

306 The use of Lovenox for thromboprophylaxis in pregnant women with mechanical prosthetic
307 heart valves has not been adequately studied. In a clinical study of pregnant women with
308 mechanical prosthetic heart valves given enoxaparin (1 mg/kg twice daily) to reduce the risk of
309 thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading
310 to maternal and fetal death. Although a causal relationship has not been established these deaths
311 may have been due to therapeutic failure or inadequate anticoagulation. No patients in the

312 heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing
313 reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while
314 receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves
315 may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher
316 rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore,
317 frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be
318 needed [see *Use in Specific Populations (8.6)*].
319

320 **5.8 Benzyl Alcohol**

321 Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of
322 medications containing benzyl alcohol as a preservative to premature neonates has been
323 associated with a fatal "Gaspings Syndrome". Because benzyl alcohol may cross the placenta,
324 Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in
325 pregnant women and only if clearly needed [see *Use in Specific Populations (8.1)*].
326

327 **5.9 Laboratory Tests**

328 Periodic complete blood counts, including platelet count, and stool occult blood tests are
329 recommended during the course of treatment with Lovenox. When administered at
330 recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and
331 Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox
332 activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the
333 anticoagulant effect of Lovenox in patients with significant renal impairment. If during Lovenox
334 therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be
335 used to monitor the anticoagulant effects of Lovenox [see *Clinical Pharmacology (12.3)*].
336

337 **6 ADVERSE REACTIONS**

338 **6.1 Clinical Trials Experience**

339 Because clinical studies are conducted under widely varying conditions, adverse reaction rates
340 observed in the clinical studies of a drug cannot be directly compared to rates in the clinical
341 studies of another drug and may not reflect the rates observed in practice.
342

343 **Hemorrhage**

344 The incidence of major hemorrhagic complications during Lovenox treatment has been low.
345

346 The following rates of major bleeding events have been reported during clinical trials with
347 Lovenox Injection [see Tables 2 to 7].
348

349
350

Table 2
Major Bleeding Episodes Following Abdominal and Colorectal Surgery¹

Indications	Dosing Regimen	
	<u>Lovenox</u> 40 mg q.d. SC	<u>Heparin</u> 5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

351 ¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant
352 clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or
353 more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were
354 always considered major.

355
356
357

Table 3
Major Bleeding Episodes Following Hip or Knee Replacement Surgery¹

Indications	Dosing Regimen		
	<u>Lovenox</u> 40 mg q.d. SC	<u>Lovenox</u> 30 mg q12h SC	<u>Heparin</u> 15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis²		n = 786 31 (4%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis			
Peri-operative Period ³	n = 288 4 (2%)		
Extended Prophylaxis Period ⁴	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis²		n = 294 3 (1%)	n = 225 3 (1%)

358 ¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant
359 clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or
360 more units of blood products. Retroperitoneal and intracranial hemorrhages were always
361 considered major. In the knee replacement surgery trials, intraocular hemorrhages were also
362 considered major hemorrhages.

363 ² Lovenox 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up
364 to 14 days after surgery.

365 ³ Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to
366 7 days after surgery.

367 ⁴ Lovenox 40 mg SC once a day for up to 21 days after discharge.

368

369 NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours
 370 post-operative hip replacement surgery prophylactic regimens compared in clinical trials.
 371 Injection site hematomas during the extended prophylaxis period after hip replacement surgery
 372 occurred in 9% of the Lovenox patients versus 1.8% of the placebo patients.
 373

374 **Table 4**

375 **Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During**
 376 **Acute Illness¹**

Indications	Dosing Regimen		
	<u>Lovenox</u> ² 20 mg q.d. SC	<u>Lovenox</u> ² 40 mg q.d. SC	<u>Placebo</u> ²
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

377 ¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant
 378 clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥ 2 g/dL or transfusion
 379 of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always
 380 considered major although none were reported during the trial.

381 ² The rates represent major bleeding on study medication up to 24 hours after last dose.
 382

383 **Table 5**

384 **Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism**
 385 **Treatment¹**

Indication	Dosing Regimen ²		
	<u>Lovenox</u> 1.5 mg/kg q.d. SC	<u>Lovenox</u> 1 mg/kg q12h SC	<u>Heparin</u> aPTT Adjusted IV Therapy
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

386 ¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant
 387 clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or
 388 more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were
 389 always considered major.

390 ² All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of
 391 2.0 to 3.0) commencing within 72 hours of Lovenox or standard heparin therapy and
 392 continuing for up to 90 days.

393
394

Table 6
Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen	
	<u>Lovenox</u> ¹ 1 mg/kg q12h SC	<u>Heparin</u> ¹ aPTT Adjusted IV Therapy
Unstable Angina and Non-Q-Wave MI ^{2,3}	n = 1578 17 (1%)	n = 1529 18 (1%)

395

¹ The rates represent major bleeding on study medication up to 12 hours after dose.

396

² Aspirin therapy was administered concurrently (100 to 325 mg per day).

397

³ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥ 3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

401

402

403

Table 7
Major Bleeding Episodes in acute ST-segment Elevation Myocardial Infarction

Indication	Dosing Regimen	
	<u>Lovenox</u> ¹ Initial 30-mg IV bolus followed by 1 mg/kg q12h SC	<u>Heparin</u> ¹ aPTT Adjusted IV Therapy
acute ST-segment Elevation Myocardial Infarction	n = 10176 n (%)	n = 10151 n (%)
- Major bleeding (including ICH) ²	211 (2.1)	138 (1.4)
- Intracranial hemorrhages (ICH)	84 (0.8)	66 (0.7)

404

¹ The rates represent major bleeding (including ICH) up to 30 days

405

² Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by ≥ 5 g/dL. ICH were always considered major.

406

407

408

Thrombocytopenia

409

[See Warnings and Precautions (5.5)]

410

411

Elevations of Serum Aminotransferases

412

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox. Similar significant increases in aminotransferase levels have also been

413

414

415

416 observed in patients and healthy volunteers treated with heparin and other low molecular weight
 417 heparins. Such elevations are fully reversible and are rarely associated with increases in
 418 bilirubin.

419
 420 Since aminotransferase determinations are important in the differential diagnosis of myocardial
 421 infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like
 422 Lovenox should be interpreted with caution.

423 **Local Reactions**

424 Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of
 425 Lovenox.

426 **Other**

427 Other adverse effects that were thought to be possibly or probably related to treatment with
 428 Lovenox, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement
 429 surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at
 430 least 2% in the Lovenox group, are provided below [see Tables 8 to 11].

431

432

Table 8

433 **Adverse Events Occurring at $\geq 2\%$ Incidence in Lovenox-Treated Patients¹ Undergoing**
 434 **Abdominal or Colorectal Surgery**

Adverse Event	Dosing Regimen			
	Lovenox 40 mg q.d. SC n = 1228		Heparin 5000 U q8h SC n = 1234	
	Severe	Total	Severe	Total
Hemorrhage	<1	7	<1	6
Anemia	<1	3	<1	3
Ecchymosis	0	3	0	3

435 ¹ Excluding unrelated adverse events.

436

437

438

Table 9

Adverse Events Occurring at $\geq 2\%$ Incidence in Lovenox-Treated Patients¹ Undergoing Hip or Knee Replacement Surgery

Adverse Event	Dosing Regimen									
	<u>Lovenox</u> 40 mg q.d. SC				<u>Lovenox</u> 30 mg q12h SC		<u>Heparin</u> 15,000 U/24h SC		<u>Placebo</u> q12h SC	
	Peri-operative Period n = 288 ² %		Extended Prophylaxis Period n = 131 ³ %		n = 1080 %		n = 766 %		n = 115 %	
	Severe	Total	Severe	Total	Severe	Total	Severe	Total	Severe	Total
Fever	0	8	0	0	<1	5	<1	4	0	3
Hemorrhage	<1	13	0	5	<1	4	1	4	0	3
Nausea					<1	3	<1%	2	0	2
Anemia	0	16	0	<2	<1	2	2	5	<1	7
Edema					<1	2	<1	2	0	2
Peripheral edema	0	6	0	0	<1	3	<1	4	0	3

439

¹ Excluding unrelated adverse events.

440

² Data represents Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox peri-operatively in an unblinded fashion in one clinical trial.

441

442

443

³ Data represents Lovenox 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

444

445

446

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448
449

Table 10
Adverse Events Occurring at $\geq 2\%$ Incidence in Lovenox-Treated Medical Patients¹ With Severely Restricted Mobility During Acute Illness

Adverse Event	Dosing Regimen	
	<u>Lovenox</u> 40 mg q.d. SC n = 360 %	<u>Placebo</u> q.d. SC n = 362 %
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

450 ¹ Excluding unrelated and unlikely adverse events.

451
452
453
454

Table 11
Adverse Events Occurring at $\geq 2\%$ Incidence in Lovenox-Treated Patients¹ Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

Adverse Event	Dosing Regimen					
	<u>Lovenox</u> 1.5 mg/kg q.d. SC n = 298 %		<u>Lovenox</u> 1 mg/kg q12h SC n = 559 %		<u>Heparin</u> aPTT Adjusted IV Therapy n = 544 %	
	Severe	Total	Severe	Total	Severe	Total
Injection Site Hemorrhage	0	5	0	3	<1	<1
Injection Site Pain	0	2	0	2	0	0
Hematuria	0	2	0	<1	<1	2

455 ¹ Excluding unrelated adverse events.

456 **Adverse Events in Lovenox-Treated Patients With Unstable Angina or Non-Q-**
457 **Wave Myocardial Infarction:**

458 Non-hemorrhagic clinical events reported to be related to Lovenox therapy occurred at an
459 incidence of $\leq 1\%$.

460
461
462
463
464

Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox than in patients treated with IV heparin.

465 Serious adverse events with Lovenox or heparin in a clinical trial in patients with unstable angina
 466 or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox
 467 group are provided below (irrespective of relationship to drug therapy) [see Table 12].
 468

469 **Table 12**

470 **Serious Adverse Events Occurring at $\geq 0.5\%$ Incidence in Lovenox-Treated Patients With**
 471 **Unstable Angina or Non-Q-Wave Myocardial Infarction**

Adverse Event	Dosing Regimen	
	<u>Lovenox</u> 1 mg/kg q12h SC n = 1578 n (%)	<u>Heparin</u> aPTT Adjusted IV Therapy n = 1529 n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

472

473 **Adverse Reactions in Lovenox-Treated Patients With acute ST-segment Elevation**
 474 **Myocardial Infarction:**

475 In a clinical trial in patients with acute ST-segment elevation myocardial infarction, the only
 476 additional possibly related adverse reaction that occurred at a rate of at least 0.5% in the
 477 Lovenox group was thrombocytopenia (1.5%)
 478

479 **6.2 Post-Marketing Experience**

480 There have been reports of epidural or spinal hematoma formation with concurrent use of
 481 Lovenox and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-
 482 operative indwelling epidural catheter placed for analgesia or received additional drugs affecting
 483 hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic
 484 injury, including long-term or permanent paralysis.
 485

486 Local reactions at the injection site (*e.g.*, skin necrosis, nodules, inflammation, oozing), systemic
 487 allergic reactions (*e.g.*, pruritus, urticaria, anaphylactoid reactions), vesicubullous rash, rare
 488 cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytosis, and thrombocytopenia
 489 with thrombosis [see *Warnings and Precautions (5.5)*] have been reported. Very rare cases of
 490 hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked
 491 hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.
 492

493 Because these reactions are reported voluntarily from a population of uncertain size, it is not
 494 possible to estimate reliably their frequency or to establish a causal relationship to drug
 495 exposure.
 496

497

498

7 DRUG INTERACTIONS

499

Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring [see *Warnings and Precautions (5.9)*].

504

505

8 USE IN SPECIFIC POPULATIONS

506

8.1 Pregnancy

507

Pregnancy Category B

508

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes the potential of Lovenox to increase the risk of developmental abnormalities above background risk.

511

512

Fetal Risk Summary

513

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

516

517

Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox contains 15 mg benzyl alcohol per 1 mL as a preservative [see *Warnings and Precautions (5.8)*].

520

521

Clinical Considerations

522

It is not known if either dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

524

525

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see *Warnings and Precautions (5.7)* and *Use in Specific Populations (8.6)*].

529

Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

532

533

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches [see *Boxed Warning*]. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

539

540

541 Data

542 • *Human Data* - There are no adequate and well-controlled studies in pregnant women.
543 A retrospective study reviewed the records of 604 women who used enoxaparin during
544 pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic
545 events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major
546 congenital anomalies in live births occurred at rates (2.5%) similar to background rates.
547 There have been postmarketing reports of fetal death when pregnant women received Lovenox.
548 Causality for these cases has not been determined. Insufficient data, the underlying disease, and
549 the possibility of inadequate anticoagulation complicate the evaluation of these cases.

550
551 A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves
552 has been conducted [see *Warnings and Precautions* (5.7)].

553
554 • *Animal Data* - Teratology studies have been conducted in pregnant rats and rabbits at SC
555 doses of enoxaparin up to 30 mg/kg/day or 211 mg/m²/day and 410 mg/m²/day,
556 respectively. There was no evidence of teratogenic effects or fetotoxicity due to
557 enoxaparin. Because animal reproduction studies are not always predictive of human
558 response, this drug should be used during pregnancy only if clearly needed.
559

560 **8.3 Nursing Mothers**

561 It is not known whether this drug is excreted in human milk. Because many drugs are excreted
562 in human milk, caution should be exercised when Lovenox is administered to nursing women.
563

564 **8.4 Pediatric Use**

565 Safety and effectiveness of Lovenox in pediatric patients have not been established.
566

567 **8.5 Geriatric Use**

568 *Prevention of DVT in hip, knee and abdominal surgery; treatment of DVT, Prevention of*
569 *ischemic complications of unstable angina and non-Q-Wave myocardial infarction*

570 Over 2800 patients, 65 years and older, have received Lovenox in pivotal clinical trials. The
571 efficacy of Lovenox in the geriatric (≥65 years) was similar to that seen in younger patients (<65
572 years). The incidence of bleeding complications was similar between geriatric and younger
573 patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox were employed. The
574 incidence of bleeding complications was higher in geriatric patients as compared to younger
575 patients when Lovenox was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12
576 hours. The risk of Lovenox -associated bleeding increased with age. Serious adverse events
577 increased with age for patients receiving Lovenox. Other clinical experience (including
578 postmarketing surveillance and literature reports) has not revealed additional differences in the
579 safety of Lovenox between geriatric and younger patients. Careful attention to dosing intervals
580 and concomitant medications (especially antiplatelet medications) is advised. Lovenox should
581 be used with care in geriatric patients who may show delayed elimination of enoxaparin.
582 Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to

583 decreased renal function should be considered [see *Warnings and Precautions (5.9)* and *Clinical*
584 *Pharmacology (12.3)*].

585

586 *Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)*

587 In the clinical study for treatment of acute STEMI, there was no evidence of difference in
588 efficacy between patients ≥ 75 years of age ($n = 1241$) and patients less than 75 years of age
589 ($n=9015$). Patients ≥ 75 years of age did not receive a 30 mg IV bolus prior to the normal dosage
590 regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours [see *Dosage and*
591 *Administration (2.3)*]. The incidence of bleeding complications was higher in patients ≥ 65 years
592 of age as compared to younger patients (< 65 years).

593

594 **8.6 Patients with Mechanical Prosthetic Heart Valves**

595 The use of Lovenox has not been adequately studied for thromboprophylaxis in patients with
596 mechanical prosthetic heart valves and has not been adequately studied for long-term use in this
597 patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in
598 patients with mechanical prosthetic heart valves who have received enoxaparin for
599 thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to
600 maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of
601 inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with
602 mechanical prosthetic heart valves may be at higher risk for thromboembolism [see *Warnings*
603 *and Precautions (5.7)*].

604

605 **8.7 Renal Impairment**

606 In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All
607 such patients should be observed carefully for signs and symptoms of bleeding. Because
608 exposure of enoxaparin sodium is significantly increased in patients with severe renal
609 impairment (creatinine clearance < 30 mL/min), a dosage adjustment is recommended for
610 therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients
611 with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80
612 mL/min) renal impairment [see *Dosage and Administration (2.2)* and *Clinical Pharmacology*
613 *(12.3)*].

614

615 **8.8 Hepatic Impairment**

616 The impact of hepatic impairment on enoxaparin's exposure and antithrombotic effect has not
617 been investigated. Caution should be exercised when administering enoxaparin to patients with
618 hepatic impairment.

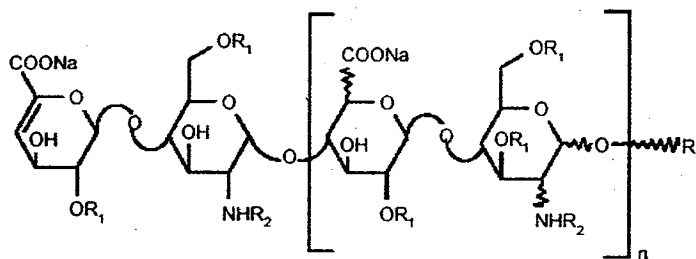
619

620 **8.9 Low-Weight Patients**

621 An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted)
622 has been observed in low-weight women (< 45 kg) and low-weight men (< 57 kg). All such
623 patients should be observed carefully for signs and symptoms of bleeding [see *Clinical*
624 *Pharmacology (12.3)*].

664

STRUCTURAL FORMULA


 $R_1 = \text{H or SO}_3\text{Na and } R_2 = \text{SO}_3\text{Na or COCH}_3$

665

R	$X^* = 15 \text{ to } 25\%$		666 667 668 669 670 671 672
	100 - X	H	673 674 675

676

677

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

678

679

Lovenox 100 mg/mL Concentration contains 10 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1000 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

682

683

Lovenox 150 mg/mL Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

686

687

The Lovenox prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection. The multiple-dose vial contains 15 mg benzyl alcohol per 1 mL as a preservative. [See *Dosage and Administration* (2) and *How Supplied* (18) for dosage unit descriptions].

691

692

12 CLINICAL PHARMACOLOGY

693

12.1 Mechanism of Action

694

Enoxaparin is a low molecular weight heparin which has antithrombotic properties.

695

696 **12.2 Pharmacodynamics**

697 In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a
698 higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean \pm SD, 14.0 ± 3.1) (based on areas
699 under anti-Factor activity versus time curves) compared to the ratios observed for heparin
700 (mean \pm SD, 1.22 ± 0.13). Increases of up to 1.8 times the control values were seen in the
701 thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1
702 mg/kg dose (100 mg / mL concentration), administered SC every 12 hours to patients in a large
703 clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n = 1607).
704 A 30-mg IV bolus immediately followed by a 1 mg/kg SC administration resulted in aPTT post-
705 injection values of 50 seconds. The average aPTT prolongation value on Day 1 was about 16%
706 higher than on Day 4.
707

708 **12.3 Pharmacokinetics**

709 Absorption. Pharmacokinetic trials were conducted using the 100 mg/ml formulation. Maximum
710 anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection
711 of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 μ g/mL) and 0.38
712 IU/mL (3.83 μ g/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively.
713 Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with
714 unstable angina receiving 1 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability
715 of enoxaparin, after 1.5 mg/kg given SC, based on anti-Factor Xa activity is approximately 100%
716 in healthy subjects.
717

718 A 30 mg IV bolus immediately followed by a 1 mg/kg SC every 12 hours provided initial peak
719 anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 84% of
720 steady-state levels. Steady state is achieved on the second day of treatment.
721

722 Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges [see
723 *Dosage and Administration (2)*]. After repeated subcutaneous administration of 40 mg once
724 daily and 1.5 mg/kg once-daily regimens in healthy volunteers, the steady state is reached on day
725 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state
726 enoxaparin activity levels are well predicted by single-dose pharmacokinetics. After repeated
727 subcutaneous administration of the 1 mg/kg twice daily regimen, the steady state is reached from
728 day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough
729 levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium
730 pharmacokinetics, this difference in steady state is expected and within the therapeutic range.
731

732 Although not studied clinically, the 150 mg/mL concentration of enoxaparin sodium is projected
733 to result in anticoagulant activities similar to those of 100 mg/mL and 200 mg/mL concentrations
734 at the same enoxaparin dose. When a daily 1.5 mg/kg SC injection of enoxaparin sodium was
735 given to 25 healthy male and female subjects using a 100 mg/mL or a 200 mg/mL concentration
736 the following pharmacokinetic profiles were obtained [see Table 13]:
737

Table 13

**Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg SC Once Daily Doses of
Enoxaparin Sodium Using 100 mg/mL or 200 mg/mL Concentrations**

	Concentration	Anti-Xa	Anti-IIa	Heptest	aPTT
A_{max} (IU/mL or Δ sec)	100 mg/mL	1.37 (\pm 0.23)	0.23 (\pm 0.05)	105 (\pm 17)	19 (\pm 5)
	200 mg/mL	1.45 (\pm 0.22)	0.26 (\pm 0.05)	111 (\pm 17)	22 (\pm 7)
	90% CI	102-110%		102-111%	
t_{max}^{**} (h)	100 mg/mL	3 (2-6)	4 (2-5)	2.5 (2-4.5)	3 (2-4.5)
	200 mg/mL	3.5 (2-6)	4.5 (2.5-6)	3.3 (2-5)	3 (2-5)
AUC (ss) (h*IU/mL or h* Δ sec)	100 mg/mL	14.26 (\pm 2.93)	1.54 (\pm 0.61)	1321 (\pm 219)	
	200 mg/mL	15.43 (\pm 2.96)	1.77 (\pm 0.67)	1401 (\pm 227)	
	90% CI	105-112%		103-109%	

*Means \pm SD at Day 5 and 90% Confidence Interval (CI) of the ratio

**Median (range)

739

740 Distribution. The volume of distribution of anti-Factor Xa activity is about 4.3 L.

741

742 Elimination. Following intravenous (IV) dosing, the total body clearance of enoxaparin is 26
743 mL/min. After IV dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc , 40% of
744 radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours.
745 Elimination half-life based on anti-Factor Xa activity was 4.5 hours after a single SC dose to
746 about 7 hours after repeated dosing. Significant anti-Factor Xa activity persists in plasma for
747 about 12 hours following a 40 mg SC once a day dose.

748

749 Following SC dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min.

750

751 Metabolism. Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or
752 depolymerization to lower molecular weight species with much reduced biological potency.
753 Renal clearance of active fragments represents about 10% of the administered dose and total
754 renal excretion of active and non-active fragments 40% of the dose.

755

756 Special Populations

757 Gender: Apparent clearance and A_{max} derived from anti-Factor Xa values following single SC
758 dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the

759 gender difference in these parameters has not been conclusively identified; however, body
760 weight may be a contributing factor.

761

762 *Geriatric:* Apparent clearance and A_{\max} derived from anti-Factor Xa values following single and
763 multiple SC dosing in geriatric subjects were close to those observed in young subjects.
764 Following once a day SC dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor
765 Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC
766 value. [see *Dosage and Administration (2.3)* and *Use in Specific Populations (8.5)*].

767

768 *Renal Impairment:* A linear relationship between anti-Factor Xa plasma clearance and creatinine
769 clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin
770 sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at
771 steady-state, is marginally increased in mild (creatinine clearance 50–80 mL/min) and moderate
772 (creatinine clearance 30–50 mL/min) renal impairment after repeated subcutaneous 40 mg once-
773 daily doses. In patients with severe renal impairment (creatinine clearance <30 mL/min), the
774 AUC at steady state is significantly increased on average by 65% after repeated subcutaneous 40
775 mg once-daily doses [see *Dosage and Administration (2.2)* and *Use in Specific Populations*
776 *(8.7)*].

777

778 *Hemodialysis:* In a single study, elimination rate appeared similar but AUC was two-fold higher
779 than control population, after a single 0.25 or 0.5 mg/kg intravenous dose.

780

781 *Hepatic Impairment:* Studies with enoxaparin in patients with hepatic impairment have not been
782 conducted and the impact of hepatic impairment on the exposure to enoxaparin is unknown [see
783 *Use in Specific Populations (8.8)*].

784

785 *Weight:* After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-Factor Xa
786 activity is marginally higher at steady-state in obese healthy volunteers (BMI 30–48 kg/m²)
787 compared to non-obese control subjects, while A_{\max} is not increased.

788

789 When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 40
790 mg dose, that anti-Factor Xa exposure is 52% higher in low-weight women (<45 kg) and 27%
791 higher in low-weight men (<57 kg) when compared to normal weight control subjects [see *Use*
792 *in Specific Populations (8.9)*].

793

794 *Pharmacokinetic interaction:* No pharmacokinetic interaction was observed between enoxaparin
795 and thrombolytics when administered concomitantly.

796

797 **13 NONCLINICAL TOXICOLOGY**

798 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

799 No long-term studies in animals have been performed to evaluate the carcinogenic potential of
800 enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse
801 lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and
802 the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no
803 effect on fertility or reproductive performance of male and female rats at SC doses up to 20

804 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or
 805 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of
 806 1.8 m²).

807

808 **13.2 Animal Toxicology**

809 A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity
 810 were ataxia, decreased motility, dyspnea, cyanosis, and coma.

811

812 **14 CLINICAL TRIALS EXPERIENCE**

813 **14.1 Prophylaxis of Deep Vein Thrombosis (DVT) Following Abdominal Surgery in**
 814 **Patients at Risk for Thromboembolic Complications**

815 Abdominal surgery patients at risk include those who are over 40 years of age, obese,
 816 undergoing surgery under general anesthesia lasting longer than 30 minutes or who have
 817 additional risk factors such as malignancy or a history of DVT or pulmonary embolism.

818 In a double-blind, parallel group study of patients undergoing elective cancer surgery of the
 819 gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the
 820 study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67
 821 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4%
 822 Asian and 0.4% others. Lovenox 40 mg SC, administered once a day, beginning 2 hours prior to
 823 surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5000
 824 U every 8 hours SC in reducing the risk of DVT. The efficacy data are provided below [see
 825 Table 14].

826

827

828

Table 14
Efficacy of Lovenox in the Prophylaxis of DVT Following Abdominal Surgery

Indication	Dosing Regimen	
	Lovenox 40 mg q.d. SC n (%)	Heparin 5000 U q8h SC n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures		
Total VTE ¹ (%)	56 (10.1) (95% CI ² : 8 to 13)	63 (11.3) (95% CI: 9 to 14)
DVT Only (%)	54 (9.7) (95% CI: 7 to 12)	61 (10.9) (95% CI: 8 to 13)

829

830

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832

833

834

¹ VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.

² CI = Confidence Interval

In a second double-blind, parallel group study, Lovenox 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in patients undergoing colorectal surgery (one-third with

835 cancer). A total of 1347 patients were randomized in the study and all patients were treated.
 836 Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8%
 837 women. Treatment was initiated approximately 2 hours prior to surgery and continued for
 838 approximately 7 to 10 days after surgery. The efficacy data are provided below [see Table 15].
 839

840
 841
 842

Table 15
Efficacy of Lovenox in the Prophylaxis of Deep Vein Thrombosis Following Colorectal Surgery

Indication	Dosing Regimen	
	<u>Lovenox</u> 40 mg q.d. SC n (%)	<u>Heparin</u> 5000 U q8h SC n (%)
All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures		
Total VTE ¹ (%)	48 (7.1) (95% CI ² : 5 to 9)	45 (6.7) (95% CI: 5 to 9)
DVT Only (%)	47 (7.0) (95% CI: 5 to 9)	44 (6.5) (95% CI: 5 to 8)

843 ¹ VTE = Venous thromboembolic events which included DVT, PE, and death considered to be
 844 thromboembolic in origin.

845 ² CI = Confidence Interval

846

847 **14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement** 848 **Surgery**

849 Lovenox has been shown to reduce the risk of post-operative deep vein thrombosis (DVT)
 850 following hip or knee replacement surgery.

851

852 In a double-blind study, Lovenox 30 mg every 12 hours SC was compared to placebo in patients
 853 with hip replacement. A total of 100 patients were randomized in the study and all patients were
 854 treated. Patients ranged in age from 41 to 84 years (mean age 67.1 years) with 45% men and
 855 55% women. After hemostasis was established, treatment was initiated 12 to 24 hours after
 856 surgery and was continued for 10 to 14 days after surgery. The efficacy data are provided below
 857 [see Table 16].

858
859
860
861

Table 16
Efficacy of Lovenox in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

Indication	Dosing Regimen	
	Lovenox 30 mg q12h SC n (%)	Placebo q12h SC n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)
Treatment Failures		
Total DVT (%)	5 (10) ¹	23 (46)
Proximal DVT (%)	1 (2) ²	11 (22)

862 ¹ p value versus placebo = 0.0002

863 ² p value versus placebo = 0.0134

864

865 A double-blind, multicenter study compared three dosing regimens of Lovenox in patients with
866 hip replacement. A total of 572 patients were randomized in the study and 568 patients were
867 treated. Patients ranged in age from 31 to 88 years (mean age 64.7 years) with 63% men and
868 37% women. Patients were 93% Caucasian, 6% Black, <1% Asian, and 1% others. Treatment
869 was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The
870 efficacy data are provided below [see Table 17].

871

872

Table 17
Efficacy of Lovenox in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

873

874

Indication	Dosing Regimen		
	10 mg q.d. SC n (%)	30 mg q12h SC n (%)	40 mg q.d. SC n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)
Treatment Failures			
Total DVT (%)	40 (25)	22 (11) ¹	27 (14)
Proximal DVT (%)	17 (11)	8 (4) ²	9 (5)

875 ¹ p value versus Lovenox 10 mg once a day = 0.0008

876 ² p value versus Lovenox 10 mg once a day = 0.0168

877

878 There was no significant difference between the 30 mg every 12 hours and 40 mg once a day
879 regimens. In a double-blind study, Lovenox 30 mg every 12 hours SC was compared to placebo
880 in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the
881 study and 131 patients were treated, of which 99 had total knee replacement and 32 had either
882 unicompartmental knee replacement or tibial osteotomy. The 99 patients with total knee
883 replacement ranged in age from 42 to 85 years (mean age 70.2 years) with 36.4% men and
884 63.6% women. After hemostasis was established, treatment was initiated 12 to 24 hours after

885 surgery and was continued up to 15 days after surgery. The incidence of proximal and total DVT
 886 after surgery was significantly lower for Lovenox compared to placebo. The efficacy data are
 887 provided below [see Table 18].

888
 889
 890
 891

Table 18
Efficacy of Lovenox in the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery

Indication	Dosing Regimen	
	Lovenox 30 mg q12h SC n (%)	Placebo q12h SC n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures		
Total DVT (%)	5 (11) ¹ (95% CI ² : 1 to 21)	32 (62) (95% CI: 47 to 76)
Proximal DVT (%)	0 (0) ³ (95% Upper CL ⁴ : 5)	7 (13) (95% CI: 3 to 24)

892 ¹ p value versus placebo = 0.0001

893 ² CI = Confidence Interval

894 ³ p value versus placebo = 0.013

895 ⁴ CL = Confidence Limit

896

897 Additionally, in an open-label, parallel group, randomized clinical study, Lovenox 30 mg every
 898 12 hours SC in patients undergoing elective knee replacement surgery was compared to heparin
 899 5000 U every 8 hours SC. A total of 453 patients were randomized in the study and all were
 900 treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and
 901 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.6% others. Treatment was
 902 initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was
 903 significantly lower for Lovenox compared to heparin.

904

905 Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery: In a study
 906 of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated,
 907 while hospitalized, with Lovenox 40 mg SC, initiated up to 12 hours prior to surgery for the
 908 prophylaxis of post-operative DVT. At the end of the peri-operative period, all patients
 909 underwent bilateral venography. In a double-blind design, those patients with no venous
 910 thromboembolic disease were randomized to a post-discharge regimen of either Lovenox 40 mg
 911 (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. A total of 179 patients were
 912 randomized in the double-blind phase of the study and all patients were treated. Patients ranged
 913 in age from 47 to 87 years (mean age 69.4 years) with 57% men and 43% women. In this
 914 population of patients, the incidence of DVT during extended prophylaxis was significantly
 915 lower for Lovenox compared to placebo. The efficacy data are provided below [see Table 19].

916
917
918
919

Table 19.
Efficacy of Lovenox in the Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

Indication (Post-Discharge)	Post-Discharge Dosing Regimen	
	<u>Lovenox</u> 40 mg q.d. SC n (%)	<u>Placebo</u> q.d. SC n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Treatment Failures		
Total DVT (%)	6 (7) ¹ (95% CI ² : 3 to 14)	18 (20) (95% CI: 12 to 30)
Proximal DVT (%)	5 (6) ³ (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)

920 ¹ p value versus placebo = 0.008

921 ² CI= Confidence Interval

922 ³ p value versus placebo = 0.537

923

924 In a second study, patients undergoing hip replacement surgery were treated, while hospitalized,
925 with Lovenox 40 mg SC, initiated up to 12 hours prior to surgery. All patients were examined
926 for clinical signs and symptoms of venous thromboembolic (VTE) disease. In a double-blind
927 design, patients without clinical signs and symptoms of VTE disease were randomized to a post-
928 discharge regimen of either Lovenox 40 mg (n = 131) once a day SC or to placebo (n = 131) for
929 3 weeks. A total of 262 patients were randomized in the study double-blind phase and all
930 patients were treated. Patients ranged in age from 44 to 87 years (mean age 68.5 years) with
931 43.1% men and 56.9% women. Similar to the first study the incidence of DVT during extended
932 prophylaxis was significantly lower for Lovenox compared to placebo, with a statistically
933 significant difference in both total DVT (Lovenox 21 [16%] versus placebo 45 [34%]; p = 0.001)
934 and proximal DVT (Lovenox 8 [6%] versus placebo 28 [21%]; p = <0.001).

935

936 **14.3 Prophylaxis of Deep Vein Thrombosis (DVT) In Medical Patients with**
937 **Severely Restricted Mobility During Acute Illness**

938 In a double blind multicenter, parallel group study, Lovenox 20 mg or 40 mg once a day SC was
939 compared to placebo in the prophylaxis of DVT in medical patients with severely restricted
940 mobility during acute illness (defined as walking distance of <10 meters for ≤3 days). This study
941 included patients with heart failure (NYHA Class III or IV); acute respiratory failure or
942 complicated chronic respiratory insufficiency (not requiring ventilatory support); acute infection
943 (excluding septic shock); or acute rheumatic disorder [acute lumbar or sciatic pain, vertebral
944 compression (due to osteoporosis or tumor), acute arthritic episodes of the lower extremities]. A
945 total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged
946 in age from 40 to 97 years (mean age 73 years) with equal proportions of men and women.
947 Treatment continued for a maximum of 14 days (median duration 7 days). When given at a dose

948 of 40 mg once a day SC, Lovenox significantly reduced the incidence of DVT as compared to
 949 placebo. The efficacy data are provided below [see Table 20].
 950

951 **Table 20**
 952 **Efficacy of Lovenox in the Prophylaxis of Deep Vein Thrombosis in Medical Patients With**
 953 **Severely Restricted Mobility During Acute Illness**

Indication	Dosing Regimen		
	<u>Lovenox</u> 20 mg q.d. SC n (%)	<u>Lovenox</u> 40 mg q.d. SC, n (%)	<u>Placebo</u> n (%)
All Treated Medical Patients During Acute Illness	351 (100)	360 (100)	362 (100)
Treatment Failure ¹			
Total VTE ² (%)	43 (12.3)	16 (4.4)	43 (11.9)
Total DVT (%)	43 (12.3) (95% CI ³ 8.8 to 15.7)	16 (4.4) (95% CI ³ 2.3 to 6.6)	41 (11.3) (95% CI ³ 8.1 to 14.6)
Proximal DVT (%)	13 (3.7)	5 (1.4)	14 (3.9)

954 ¹ Treatment failures during therapy, between Days 1 and 14.

955 ² VTE = Venous thromboembolic events which included DVT, PE, and death considered to be
 956 thromboembolic in origin.

957 ³ CI = Confidence Interval

958

959 At approximately 3 months following enrollment, the incidence of venous thromboembolism
 960 remained significantly lower in the Lovenox 40 mg treatment group versus the placebo treatment
 961 group.

962 **14.4 Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary**
 963 **Embolism (PE)**

964 In a multicenter, parallel group study, 900 patients with acute lower extremity DVT with or
 965 without PE were randomized to an inpatient (hospital) treatment of either (i) Lovenox 1.5 mg/kg
 966 once a day SC, (ii) Lovenox 1 mg/kg every 12 hours SC, or (iii) heparin IV bolus (5000 IU)
 967 followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A
 968 total of 900 patients were randomized in the study and all patients were treated. Patients ranged
 969 in age from 18 to 92 years (mean age 60.7 years) with 54.7% men and 45.3% women. All
 970 patients also received warfarin sodium (dose adjusted according to PT to achieve an International
 971 Normalization Ratio [INR] of 2.0 to 3.0), commencing within 72 hours of initiation of Lovenox
 972 or standard heparin therapy, and continuing for 90 days. Lovenox or standard heparin therapy
 973 was administered for a minimum of 5 days and until the targeted warfarin sodium INR was
 974 achieved. Both Lovenox regimens were equivalent to standard heparin therapy in reducing the
 975 risk of recurrent venous thromboembolism (DVT and/or PE). The efficacy data are provided
 976 below [see Table 21].

977
978
979
980

Table 21
Efficacy of Lovenox in Treatment of Deep Vein Thrombosis
With or Without Pulmonary Embolism

Indication	Dosing Regimen ¹		
	<u>Lovenox</u> 1.5 mg/kg q.d. SC n (%)	<u>Lovenox</u> 1 mg/kg q12h SC n (%)	<u>Heparin</u> aPTT Adjusted IV Therapy n (%)
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Patient Outcome			
Total VTE ² (%)	13 (4.4) ³	9 (2.9) ³	12 (4.1)
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

981
982
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987

¹ All patients were also treated with warfarin sodium commencing within 72 hours of Lovenox or standard heparin therapy.

² VTE = venous thromboembolic event (DVT and/or PE).

³ The 95% Confidence Intervals for the treatment differences for total VTE were:

Lovenox once a day versus heparin (-3.0 to 3.5)

Lovenox every 12 hours versus heparin (-4.2 to 1.7).

988 Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT
989 were randomized to Lovenox or heparin. Patients who could not receive outpatient therapy were
990 excluded from entering the study. Outpatient exclusion criteria included the following: inability
991 to receive outpatient heparin therapy because of associated co-morbid conditions or potential for
992 non-compliance and inability to attend follow-up visits as an outpatient because of geographic
993 inaccessibility. Eligible patients could be treated in the hospital, but ONLY Lovenox patients
994 were permitted to go home on therapy (72%). A total of 501 patients were randomized in the
995 study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8
996 years) with 60.5% men and 39.5% women. Patients were randomized to either Lovenox 1 mg/kg
997 every 12 hours SC or heparin IV bolus (5000 IU) followed by a continuous infusion
998 administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also
999 received warfarin sodium as described in the previous study. Lovenox or standard heparin
1000 therapy was administered for a minimum of 5 days. Lovenox was equivalent to standard heparin
1001 therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are
1002 provided below [see Table 22].

1003
1004
1005

Table 22
Efficacy of Lovenox in Treatment of Deep Vein Thrombosis

Indication	Dosing Regimen¹	
	Lovenox 1 mg/kg q12h SC n (%)	Heparin aPTT Adjusted IV Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome		
Total VTE ² (%)	13 (5.3) ³	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	3 (1.2)

1006 ¹ All patients were also treated with warfarin sodium commencing on the evening of the second
1007 day of Lovenox or standard heparin therapy.

1008 ² VTE = venous thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary
1009 embolism [PE]).

1010 ³ The 95% Confidence Intervals for the treatment difference for total VTE was: Lovenox versus
1011 heparin
1012 (- 5.6 to 2.7).
1013

1014 **14.5 Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave**
1015 **Myocardial Infarction**

1016 In a multicenter, double-blind, parallel group study, patients who recently experienced unstable
1017 angina or non-Q-wave myocardial infarction were randomized to either Lovenox 1 mg/kg every
1018 12 hours SC or heparin IV bolus (5000 U) followed by a continuous infusion (adjusted to
1019 achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study, and
1020 3107 patients were treated. Patients ranged in age from 25-94 years (median age 64 years), with
1021 33.4% of patients female and 66.6% male. Race was distributed as follows: 89.8% Caucasian,
1022 4.8% Black, 2.0% Asian, and 3.5% other. All patients were also treated with aspirin 100 to 325
1023 mg per day. Treatment was initiated within 24 hours of the event and continued until clinical
1024 stabilization, revascularization procedures, or hospital discharge, with a maximal duration of 8
1025 days of therapy. The combined incidence of the triple endpoint of death, myocardial infarction,
1026 or recurrent angina was lower for Lovenox compared with heparin therapy at 14 days after
1027 initiation of treatment. The lower incidence of the triple endpoint was sustained up to 30 days
1028 after initiation of treatment. These results were observed in an analysis of both all-randomized
1029 and all-treated patients. The efficacy data are provided below [see Table 23].

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1032
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1034

Table 23
Efficacy of Lovenox in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction
(Combined Endpoint of Death, Myocardial Infarction, or Recurrent Angina)

Indication	Dosing Regimen¹		Reduction (%)	p Value
	Lovenox 1mg/kg q12h SC n (%)	Heparin aPTT Adjusted IV Therapy n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint²				
48 Hours	96 (6.1)	112 (7.3)	1.2	0.120
14 Days	261 (16.5)	303 (19.8)	3.3	0.017
30 Days	313 (19.8)	358 (23.4)	3.6	0.014

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1036
1037
1038

¹ All patients were also treated with aspirin 100 to 325 mg per day.

² Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

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1040
1041
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1043

The combined incidence of death or myocardial infarction at all time points was lower for Lovenox compared to standard heparin therapy, but did not achieve statistical significance. The efficacy data are provided below [see Table 24].

Table 24
Efficacy of Lovenox in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction
(Combined Endpoint of Death or Myocardial Infarction)

Indication	Dosing Regimen¹		Reduction (%)	p Value
	Lovenox 1 mg/kg q12h SC n (%)	Heparin aPTT Adjusted IV Therapy n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint²				
48 Hours	16 (1.0)	20 (1.3)	0.3	0.126
14 Days	76 (4.8)	93 (6.1)	1.3	0.115
30 Days	96 (6.1)	118 (7.7)	1.6	0.069

1047

¹ All patients were also treated with aspirin 100 to 325 mg per day.

1048 ² Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days
1049 (median duration of 2.6 days).

1050

1051 In a survey one year following treatment, with information available for 92% of enrolled
1052 patients, the combined incidence of death, myocardial infarction, or recurrent angina remained
1053 lower for Lovenox versus heparin (32.0% vs 35.7%).

1054

1055 Urgent revascularization procedures were performed less frequently in the Lovenox group as
1056 compared to the heparin group, 6.3% compared to 8.2% at 30 days ($p = 0.047$).

1057

1058 **14.6 Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)**

1059 In a multicenter, double-blind, double-dummy, parallel group study, patients with STEMI who
1060 were to be hospitalized within 6 hours of onset and were eligible to receive fibrinolytic therapy
1061 were randomized in a 1:1 ratio to receive either Lovenox or unfractionated heparin.

1062

1063 Study medication was initiated between 15 minutes before and 30 minutes after the initiation of
1064 fibrinolytic therapy. Unfractionated heparin was administered beginning with an IV bolus of 60
1065 U/kg (maximum 4000 U) and followed with an infusion of 12 U/kg per hour (initial maximum
1066 1000 U per hour) that was adjusted to maintain an aPTT of 1.5 to 2 times the control value. The
1067 IV infusion was to be given for at least 48 hours. The enoxaparin dosing strategy was adjusted
1068 according to the patient's age and renal function. For patients younger than 75 years of age,
1069 enoxaparin was given as a single 30-mg intravenous bolus plus a 1 mg/kg SC dose followed by
1070 an SC injection of 1 mg/kg every 12 hours. For patients at least 75 years of age, the IV bolus
1071 was not given and the SC dose was reduced to 0.75 mg/kg every 12 hours. For patients with
1072 severe renal insufficiency (estimated creatinine clearance of less than 30 mL per minute), the
1073 dose was to be modified to 1 mg/kg every 24 hours. The SC injections of enoxaparin were given
1074 until hospital discharge or for a maximum of eight days (whichever came first). The mean
1075 treatment duration for enoxaparin was 6.6 days. The mean treatment duration of unfractionated
1076 heparin was 54 hours.

1077

1078 When percutaneous coronary intervention was performed during study medication period,
1079 patients received antithrombotic support with blinded study drug. For patients on enoxaparin,
1080 the PCI was to be performed on enoxaparin (no switch) using the regimen established in
1081 previous studies, *i.e.* no additional dosing, if the last SC administration was less than 8 hours
1082 before balloon inflation, IV bolus of 0.3 mg/kg enoxaparin if the last SC administration was
1083 more than 8 hours before balloon inflation

1084

1085 All patients were treated with aspirin for a minimum of 30 days. Eighty percent of patients
1086 received a fibrin-specific agent (19% tenecteplase, 5% reteplase and 55% alteplase) and 20%
1087 received streptokinase.

1088

1089 Among 20,479 patients in the ITT population, the mean age was 60 years, and 76% were male.
1090 Racial distribution was: 87% Caucasian, 9.8% Asian, 0.2% Black, and 2.8% other. Medical
1091 history included previous MI (13%), hypertension (44%), diabetes (15%) and angiographic
1092 evidence of CAD (5%). Concomitant medication included aspirin (95%), beta-blockers (86%),

1093 ACE inhibitors (78%), statins (70%) and clopidogrel (27%). The MI at entry was anterior in
 1094 43%, non-anterior in 56%, and both in 1%.

1095
 1096 The primary efficacy end point was the composite of death from any cause or myocardial re-
 1097 infarction in the first 30 days after randomization. Total follow-up was one year.

1098
 1099 The rate of the primary efficacy end point (death or myocardial re-infarction) was 9.9% in the
 1100 enoxaparin group, and 12.0% in the unfractionated heparin group, a 17% reduction in the relative
 1101 risk, (P=0.000003). [see Table 25]

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Table 25

1104 **Efficacy of Lovenox Injection in the treatment of acute ST-segment Elevation Myocardial**
 1105 **Infarction**

	Enoxaparin (N=10,256)	UFH (N=10,223)	Relative Risk (95% CI)	P Value
Outcome at 48 hours				
Death or Myocardial Re-infarction	n (%) 478 (4.7)	n (%) 531 (5.2)	0.90 (0.80 to 1.01)	0.08
Death	383 (3.7)	390 (3.8)	0.98 (0.85 to 1.12)	0.76
Myocardial Re-infarction	102 (1.0)	156 (1.5)	0.65 (0.51 to 0.84)	<0.001
Urgent Revascularization	74 (0.7)	96 (0.9)	0.77 (0.57 to 1.04)	0.09
Death or Myocardial Re-infarction or Urgent Revascularization	548 (5.3)	622 (6.1)	0.88 (0.79 to 0.98)	0.02
Outcome at 8 Days				
Death or Myocardial Re-infarction	740 (7.2)	954 (9.3)	0.77 (0.71 to 0.85)	<0.001
Death	559 (5.5)	605 (5.9)	0.92 (0.82 to 1.03)	0.15
Myocardial Re-infarction	204 (2.0)	379 (3.7)	0.54 (0.45 to 0.63)	<0.001
Urgent Revascularization	145 (1.4)	247 (2.4)	0.59 (0.48 to 0.72)	<0.001
Death or Myocardial Re-infarction or Urgent Revascularization	874 (8.5)	1181 (11.6)	0.74 (0.68 to 0.80)	<0.001
Outcome at 30 Days				
Primary efficacy endpoint (Death or Myocardial Re-infarction)	1017 (9.9)	1223 (12.0)	0.83 (0.77 to 0.90)	0.000003
Death	708 (6.9)	765 (7.5)	0.92 (0.84 to 1.02)	0.11
Myocardial Re-infarction	352 (3.4)	508 (5.0)	0.69 (0.60 to 0.79)	<0.001
Urgent Revascularization	213 (2.1)	286 (2.8)	0.74 (0.62 to 0.88)	<0.001
Death or Myocardial Re-infarction or Urgent Revascularization	1199 (11.7)	1479 (14.5)	0.81 (0.75 to 0.87)	<0.001

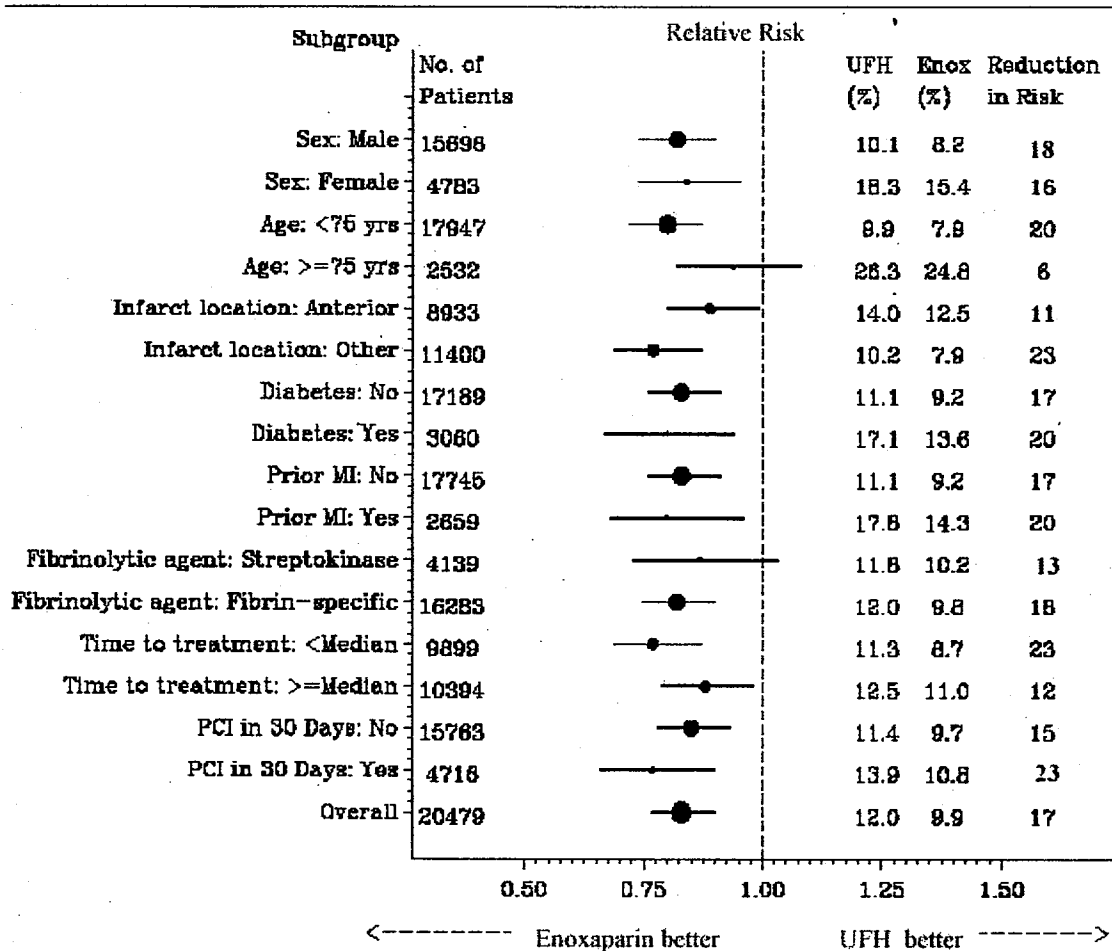
Note: Urgent revascularization denotes episodes of recurrent myocardial ischemia (without infarction) leading to the clinical decision to perform coronary revascularization during the same hospitalization. CI denotes confidence intervals.

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The beneficial effect of enoxaparin on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, fibrinolytic agent administered, and time to treatment with study drug (see Figure 1); however, it is necessary to interpret such subgroup analyses with caution.

Figure 1. Relative Risks of and Absolute Event Rates for the Primary End Point at 30 Days in Various Subgroups *



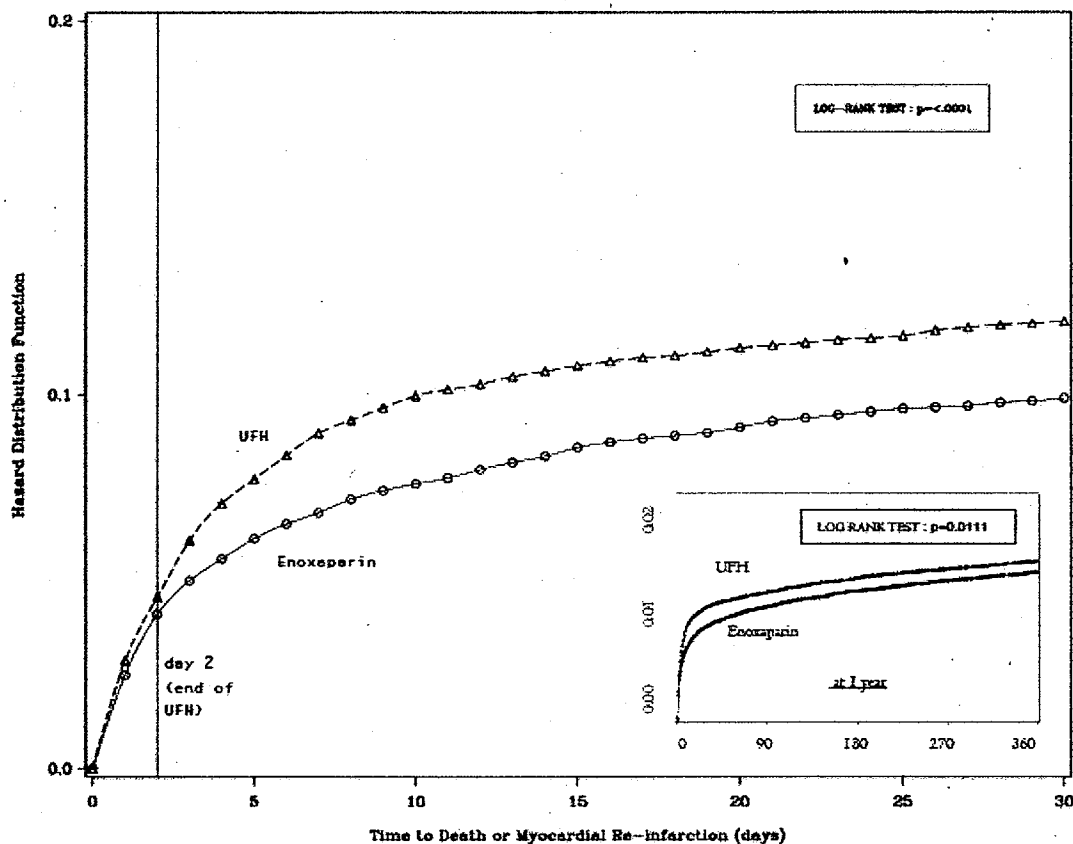
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* The primary efficacy end point was the composite of death from any cause or myocardial re-infarction in the first 30 days. The overall treatment effect of enoxaparin as compared to the unfractionated heparin is shown at the bottom of the figure. For each subgroup, the circle is proportional to the number and represents the point estimate of the treatment effect and the horizontal lines represent the 95 percent confidence intervals. Fibrin-specific fibrinolytic agents included alteplase, tenecteplase and reteplase. Time to treatment indicates the time from the onset of symptoms to the administration of study drug (median, 3.2 hours).

The beneficial effect of enoxaparin on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2).

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Figure 2 - Kaplan-Meier plot - death or myocardial re-infarction at 30 days - ITT population



Number at Risk:

Enox	9676	9481	9387	9323	9265	9236
UFH	9493	9225	9126	9074	9036	8996

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1132 There is a trend in favor of enoxaparin during the first 48 hours, but most of the treatment
1133 difference is attributed to a step increase in the event rate in the UFH group at 48 hours (seen in
1134 Figure 2), an effect that is more striking when comparing the event rates just prior to and just
1135 subsequent to actual times of discontinuation. These results provide evidence that UFH was
1136 effective and that it would be better if used longer than 48 hours. There is a similar increase in
1137 endpoint event rate when enoxaparin was discontinued, suggesting that it too was discontinued
1138 too soon in this study.

1139

1140 The rates of major hemorrhages (defined as requiring 5 or more units of blood for transfusion, or
1141 15% drop in hematocrit or clinically overt bleeding, including intracranial hemorrhage) at 30
1142 days were 2.1% in the enoxaparin group and 1.4% in the unfractionated heparin group. The rates
1143 of intracranial hemorrhage at 30 days were 0.8% in the enoxaparin group 0.7% in the
1144 unfractionated heparin group. The 30-day rate of the composite endpoint of death, myocardial
1145 re-infarction or ICH (a measure of net clinical benefit) was significantly lower in the enoxaparin
1146 group (10.1%) as compared to the heparin group (12.2%).

1148

1149 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1150 Lovenox is available in two concentrations [see Tables 26 and 27]:

Table 26

100 mg/mL Concentration

Dosage Unit / Strength ¹	Anti-Xa Activity ²	Package Size (per carton)	Label Color	NDC # 0075-
Prefilled Syringes³				
30 mg / 0.3 mL	3000 IU	10 syringes	Medium Blue	0624-30
40 mg / 0.4 mL	4000 IU	10 syringes	Yellow	0620-40
Graduated Prefilled Syringes³				
60 mg / 0.6 mL	6000 IU	10 syringes	Orange	0621-60
80 mg / 0.8 mL	8000 IU	10 syringes	Brown	0622-80
100 mg / 1 mL	10,000 IU	10 syringes	Black	0623-00
Multiple-Dose Vial⁴				
300 mg / 3 mL	30,000 IU	1 vial	Red	0626-03

1151 ¹ Strength represents the number of milligrams of enoxaparin sodium in Water for Injection.
 1152 Lovenox 30 and 40 mg prefilled syringes, and 60, 80, and 100 mg graduated prefilled syringes
 1153 each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection.**

1154 ² Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low
 1155 Molecular Weight Heparin Reference Standard.

1156 ³ Each Lovenox syringe is affixed with a 27 gauge x 1/2 inch needle.

1157 ⁴ Each Lovenox multiple-dose vial contains 15 mg benzyl alcohol per 1 mL as a preservative.
 1158

Table 27

150 mg/mL Concentration

Dosage Unit / Strength ¹	Anti-Xa Activity ²	Package Size (per carton)	Syringe Label Color	NDC # 0075-
Graduated Prefilled Syringes³				
120 mg / 0.8 mL	12,000 IU	10 syringes	Purple	2912-01
150 mg / 1 mL	15,000 IU	10 syringes	Navy Blue	2915-01

1159 ¹ Strength represents the number of milligrams of enoxaparin sodium in Water for Injection.
 1160 Lovenox 120 and 150 mg graduated prefilled syringes contain **15 mg enoxaparin sodium per**
 1161 **0.1 mL Water for Injection.**

1162 ² Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low
 1163 Molecular Weight Heparin Reference Standard.

1164 ³ Each Lovenox graduated prefilled syringe is affixed with a 27 gauge x 1/2 inch needle.
 1165

1166 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room
1167 Temperature].

1168

1169 Do not store the multiple-dose vials for more than 28 days after the first use

1170

1171 **Keep out of the reach of children.**

1172

1173 **17 PATIENT COUNSELING INFORMATION**

1174 Patients should be told that it may take them longer than usual to stop bleeding, that they may
1175 bruise and/or bleed more easily when they are treated with Lovenox, and that they should report
1176 any unusual bleeding or bruising to their physician [see *Warnings and Precautions (5.1, 5.5)*].

1177

1178 Patients should inform physicians and dentists that they are taking Lovenox and/or any other
1179 product known to affect bleeding before any surgery is scheduled and before any new drug is
1180 taken [see *Warnings and Precautions (5.3)*].

1181

1182 Patients should inform their physicians and dentists of all medications they are taking, including
1183 those obtained without a prescription [see *Drug Interactions (7)*].

1184

1185 sanofi-aventis U.S. LLC

1186 Bridgewater, NJ 08807

1187

1188 Multiple-dose vials are also manufactured by DSM Pharmaceuticals, Inc.

1189 Greenville, NC 27835

1190

1191 **Manufactured for:**

1192 sanofi-aventis U.S. LLC

1193 Bridgewater, NJ 08807