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 HEMATOMAS

See full prescribing information for complete boxed warning.

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery**
- **Optimal timing between the administration of Lovenox and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. (5.1, 7)

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

Contraindications (4)	10/2017
Warnings and Precautions (5.4, 5.8)	10/2017

----------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	Dose
DVT prophylaxis in abdominal surgery	40 mg subcutaneously once daily
DVT prophylaxis in knee replacement surgery	30 mg subcutaneously every 12 hours
DVT prophylaxis in hip replacement surgery	30 mg subcutaneously every 12 hours or 40 mg subcutaneously once daily
DVT prophylaxis in medical patients	40 mg subcutaneously once daily
Inpatient treatment of acute DVT with or without pulmonary embolism	1 mg/kg subcutaneously every 12 hours or 1.5 mg/kg subcutaneously once daily*
Outpatient treatment of acute DVT without pulmonary embolism	1 mg/kg subcutaneously every 12 hours*
Unstable angina and non–Q-wave MI	1 mg/kg subcutaneously every 12 hours (with aspirin)
Acute STEMI in patients <75 years of age [For dosing in subsequent PCI, see *Dosage and Administration (2.1)*]	30 mg single intravenous bolus plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg subcutaneously every 12 hours (with aspirin)
Acute STEMI in patients ≥75 years of age	0.75 mg/kg subcutaneously every 12 hours (no bolus) (with aspirin)

- See recommended durations for Lovenox therapy (2.1)
- *See recommendations regarding transitioning to warfarin therapy (2.1)
- Adjust the dose for patients with severe renal impairment (2.2, 8.7)

----------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)
- History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (4)
- Hypersensitivity to enoxaparin sodium (4)
- Hypersensitivity to heparin or pork products (4)
- Hypersensitivity to benzyl alcohol (for multidose formulation only) (4)

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

- Increased risk of hemorrhage: Use with caution in patients at risk (5.1)
- Percutaneous coronary revascularization: Obtain hemostasis at the puncture site before sheath removal (5.2)
- Concomitant medical conditions: Use with caution in patients with bleeding diathesis, uncontrolled arterial hypertension or history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction, or hemorrhage (5.3)
- History of heparin-induced thrombocytopenia: See Contraindications (4).Use may be considered if previous HIT episode was >100 days prior and no circulating antibodies are present (5.4)
- Thrombocytopenia: Monitor platelet count closely (5.5)
- Interchangeability with other heparins: Do not exchange with heparin or other LMWHs (5.6)
- Pregnant women with mechanical prosthetic heart valves, and their fetuses, may be at increased risk and may need more frequent monitoring and dosage adjustment (5.7)

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

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, nausea, ecchymosis, fever, edema, peripheral edema, dyspnea, confusion, and injection site pain (6.1)

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, 8.7)
- Geriatric Patients: Monitor for increased risk of bleeding (8.5)
- Patients with mechanical heart valves: Not adequately studied (8.6)
- Hepatic Impairment: Use with caution. (8.8)
- Low-Weight Patients: Observe for signs of bleeding (8.9)
- Obese Patients: Not adequately studied. Observe for thromboembolism (8.10)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in Table 1 *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

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

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

2.3 Geriatric Patients with Acute ST-Segment Elevation Myocardial Infarction

For treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, **do not use an initial intravenous bolus**. Initiate dosing with **0.75 mg/kg subcutaneously every 12 hours (maximum 75 mg for the first two doses only, followed by 0.75 mg/kg dosing for the remaining doses)** *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*.

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

2.4 Administration

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

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

Table 10: Adverse Reactions Occurring at ≥2% Incidence in Lovenox-Treated Medical Patients with Severely Restricted Mobility During Acute Illness

Adverse Reaction	Dosing Regimen	
	Lovenox 40 mg daily subcutaneously n=360 %	**Placebo** daily subcutaneously 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

Table 11: Adverse Reactions Occurring at ≥2% Incidence in Lovenox-Treated Patients Undergoing Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

Adverse Reaction	Dosing Regimen					
	Lovenox 1.5 mg/kg daily subcutaneously n=298 %		**Lovenox** 1 mg/kg q12h subcutaneously n=559 %		**Heparin** aPTT Adjusted Intravenous 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

Adverse Events in Lovenox-Treated Patients with Unstable Angina or Non–Q-Wave Myocardial Infarction

Non-hemorrhagic clinical events reported to be related to Lovenox therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic events, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with subcutaneous Lovenox than in patients treated with intravenous heparin.

Serious adverse events with Lovenox or heparin in a clinical trial in patients with unstable angina or non–Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox group are provided below (see Table 12).

Table 12: Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox-Treated Patients with Unstable Angina or Non−Q-Wave Myocardial Infarction

	Dosing Regimen	
Adverse Event	**Lovenox** 1 mg/kg q12h subcutaneously n=1578 n (%)	**Heparin** aPTT Adjusted Intravenous 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)

Adverse Reactions in Lovenox-Treated Patients with Acute ST-Segment Elevation Myocardial Infarction

In a clinical trial in patients with acute ST-segment elevation myocardial infarction, thrombocytopenia occurred at a rate of 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Lovenox. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Local reactions at the injection site (e.g. nodules, inflammation, oozing), systemic allergic reactions (e.g. pruritus, urticaria, anaphylactic/anaphylactoid reactions including shock), vesiculobullous rash, cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thrombocytopenia with thrombosis *[see Warnings and Precautions (5.5)]* have been reported.

Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues). Very rare cases of hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

Cases of headache, hemorrhagic anemia, eosinophilia, alopecia, hepatocellular and cholestatic liver injury have been reported

Osteoporosis has also been reported following long-term therapy.

7 DRUG INTERACTIONS

Whenever possible, 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 coadministration is essential, conduct close clinical and laboratory monitoring *[see Warnings and Precautions (5.9)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

All pregnancies have a background risk of birth defect, 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 the background risk.

Fetal Risk Summary

Lovenox does not cross the placenta, and is not expected to result in fetal exposure to the drug. Human data from a retrospective cohort study, which included 693 live births, suggest that Lovenox does not increase the risk of major developmental abnormalities. Based on animal data, enoxaparin is not predicted to increase the risk of major developmental abnormalities *[see Data]*.

Clinical Considerations

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)]*. 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.

All patients receiving anticoagulants, 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.

It is not known if monitoring of anti-Factor Xa activity and dose adjustment (by weight or anti-Factor Xa activity) of Lovenox affect the safety and the efficacy of the drug during pregnancy.

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)]*.

Data

Human Data

There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624

pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

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

Animal Data

Teratology studies have been conducted in pregnant rats and rabbits at subcutaneous doses of enoxaparin up to 15 times the recommended human dose (by comparison with 2 mg/kg as the maximum recommended daily dose). There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether Lovenox is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Lovenox, a decision should be made whether to discontinue nursing or discontinue Lovenox, taking into account the importance of Lovenox to the mother and the known benefits of nursing.

8.4 Pediatric Use

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

Lovenox is not approved for use in neonates or infants.

Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature neonates and low birth weight infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

Lovenox multiple-dose vials contain 15 mg/mL of benzyl alcohol (at the dose of 1.5 mg/kg twice a day, benzyl alcohol exposure in patients is 0.45 mg/kg daily) *[see Warnings and Precautions (5.8)]*.

8.5 Geriatric Use

Prevention of Deep Vein Thrombosis in Hip, Knee and Abdominal Surgery; Treatment of Deep Vein Thrombosis, Prevention of Ischemic Complications of Unstable Angina and Non–Q-wave Myocardial Infarction

Over 2800 patients, 65 years and older, have received Lovenox in pivotal clinical trials. The efficacy of Lovenox in the geriatric (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when Lovenox was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Lovenox should be used with care in geriatric patients who may show delayed elimination of enoxaparin. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.3)]*.

Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

8.6 Patients with Mechanical Prosthetic Heart Valves

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

8.7 Renal Impairment

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia *[see Adverse Reactions (6.2)]*.

8.8 Hepatic Impairment

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

8.9 Low-Weight Patients

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

8.10 Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses of Lovenox in obese patients (BMI >30 kg/m^2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

10 OVERDOSAGE

Accidental overdosage following administration of Lovenox may lead to hemorrhagic complications. Injected Lovenox may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of Lovenox may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

If at least 12 hours have elapsed since the last enoxaparin sodium injection, protamine administration may not be required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

11 DESCRIPTION

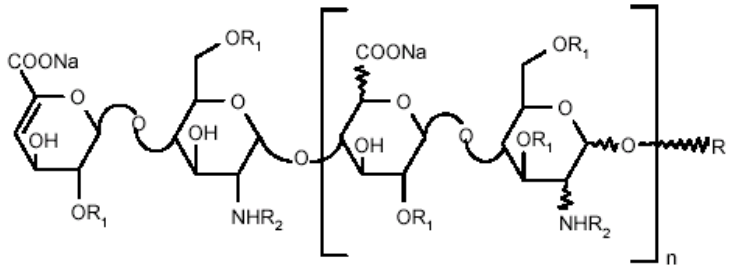
Lovenox is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin. The pH of the injection is 5.5 to 7.5.

Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of

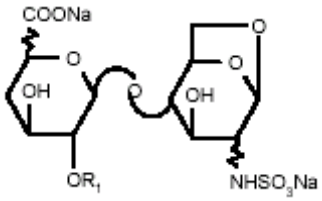
the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain. The drug substance is the sodium salt. The average molecular weight is about 4500 daltons. The molecular weight distribution is:

<2000 daltons	≤20%
2000 to 8000 daltons	≥68%
>8000 daltons	≤18%

STRUCTURAL FORMULA



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

R	**X*=15 to 25%**		**n=0 to 20**
	100-X	**H**	**n=1 to 21**

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

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.

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.

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 (16)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption

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

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

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

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

Table 13: Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg subcutaneously 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 (±0.23)	0.23 (±0.05)	105 (±17)	19 (±5)
	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	111 (±17)	22 (±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 (±2.93)	1.54 (±0.61)	1321 (±219)	
	200 mg/mL	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)	
	90% CI	105%-112%		103%-109%	

* Means ±SD at Day 5 and 90% Confidence Interval (CI) of the ratio
† Median (range)

Distribution

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

Elimination

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

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

Metabolism

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

Special Populations

Gender

Apparent clearance and A_{max} derived from anti-Factor Xa values following single subcutaneous dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters has not been conclusively identified; however, body weight may be a contributing factor.

Geriatric

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

Renal Impairment

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

Hemodialysis

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

Hepatic Impairment

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

Weight

After repeated subcutaneous 1.5 mg/kg once-daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while A_{max} is not increased.

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

Pharmacokinetic Interaction

No pharmacokinetic interaction was observed between enoxaparin and thrombolytics when administered concomitantly.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2.0

mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

13.2 Animal Toxicology and/or Pharmacology

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

13.3 Reproductive and Developmental Toxicology

Teratology studies have been conducted in pregnant rats and rabbits at subcutaneous doses of enoxaparin up to 30 mg/kg/day corresponding to 211 mg/m^2/day and 410 mg/m^2/day in rats and rabbits respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin.

14 CLINICAL STUDIES

14.1 Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications

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

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

Table 14: Efficacy of Lovenox in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

	Dosing Regimen	
Indication	**Lovenox** 40 mg daily subcutaneously n (%)	**Heparin** 5000 U q8h subcutaneously n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures		
Total VTE* (%)	56 (10.1) (95% CI†: 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)

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

† CI = Confidence Interval

In a second double-blind, parallel group study, Lovenox 40 mg subcutaneously once a day was compared to heparin 5000 U every 8 hours subcutaneously in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below (see Table 15).

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

	Dosing Regimen	
Indication	**Lovenox** 40 mg daily subcutaneously n (%)	**Heparin** 5000 U q8h subcutaneously n (%)
All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures Total VTE* (%)	48 (7.1) (95% CI†: 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)

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

† CI = Confidence Interval

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

Lovenox has been shown to reduce the risk of postoperative deep vein thrombosis (DVT) following hip or knee replacement surgery.

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

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

	Dosing Regimen	
Indication	**Lovenox** 30 mg q12h subcutaneously n (%)	**Placebo** q12h subcutaneously n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)

Treatment Failures Total DVT (%)	5 (10)*	23 (46)
Proximal DVT (%)	1 (2)†	11 (22)

* p value versus placebo = 0.0002

† p value versus placebo = 0.0134

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

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

	Dosing Regimen		
Indication	**10 mg daily subcutaneously** n (%)	**30 mg q12h subcutaneously** n (%)	**40 mg daily subcutaneously** n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)
Treatment Failures Total DVT (%)	40 (25)	22 (11)*	27 (14)
Proximal DVT (%)	17 (11)	8 (4)†	9 (5)

* p value versus Lovenox 10 mg once a day = 0.0008

† p value versus Lovenox 10 mg once a day = 0.0168

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens. In a double-blind study, Lovenox 30 mg every 12 hours subcutaneously was compared to placebo in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the study and 131 patients were treated, of which 99 had total knee replacement and 32 had either unicompartmental knee replacement or tibial osteotomy. The 99 patients with total knee replacement ranged in age from 42 to 85 years (mean age 70.2 years) with 36.4% men and 63.6% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued up to 15 days after surgery. The incidence of proximal and total DVT after surgery was significantly lower for Lovenox compared to placebo. The efficacy data are provided below (see Table 18).

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

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

* p value versus placebo = 0.0001
† CI = Confidence Interval
‡ p value versus placebo = 0.013
§ CL = Confidence Limit

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

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

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

	Post-discharge Dosing Regimen	
Indication (Post Discharge)	**Lovenox** 40 mg daily subcutaneously n (%)	**Placebo** daily subcutaneously n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Treatment Failures Total DVT (%)	6 (7)* (95% CI†: 3 to 14)	18 (20) (95% CI: 12 to 30)
Proximal DVT (%)	5 (6)‡ (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)

* p value versus placebo = 0.008
† CI= Confidence Interval
‡ p value versus placebo = 0.537

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

14.3 Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility During Acute Illness

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

Table 20: Efficacy of Lovenox in the Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility During Acute Illness

	Dosing Regimen		
	Lovenox 20 mg daily subcutaneously	**Lovenox** 40 mg daily subcutaneously	**Placebo**
Indication	n (%)	n (%)	n (%)
All Treated Medical Patients During Acute Illness	351 (100)	360 (100)	362 (100)
Treatment Failure* Total VTE† (%)	43 (12.3)	16 (4.4)	43 (11.9)
Total DVT (%)	43 (12.3) (95% CI‡ 8.8 to 15.7)	16 (4.4) (95% CI‡ 2.3 to 6.6)	41 (11.3) (95% CI‡ 8.1 to 14.6)
Proximal DVT (%)	13 (3.7)	5 (1.4)	14 (3.9)

* Treatment failures during therapy, between Days 1 and 14

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

‡ CI = Confidence Interval

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

14.4 Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

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

Table 21: Efficacy of Lovenox in Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

	Dosing Regimen*		
	Lovenox 1.5 mg/kg daily subcutaneously	**Lovenox** 1 mg/kg q12h subcutaneously	**Heparin** aPTT Adjusted Intravenous Therapy
Indication	n (%)	n (%)	n (%)
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Patient Outcome Total VTE† (%)	13 (4.4)‡	9 (2.9)‡	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)

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

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

‡ 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).

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

Table 22: Efficacy of Lovenox in Treatment of Deep Vein Thrombosis

Indication	Dosing Regimen*	
	Lovenox 1 mg/kg q12h subcutaneously n (%)	**Heparin** aPTT Adjusted Intravenous Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome Total VTE† (%)	13 (5.3)‡	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)

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

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

‡ The 95% Confidence Intervals for the treatment difference for total VTE was: Lovenox versus heparin (-5.6 to 2.7).

14.5 Prophylaxis of Ischemic Complications in Unstable Angina and Non–Q-Wave Myocardial Infarction

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

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)

	Dosing Regimen*			
Indication	**Lovenox** 1 mg/kg q12h subcutaneous n (%)	**Heparin** aPTT Adjusted Intravenous Therapy n (%)	**Reduction** (%)	**p Value**
All Treated Unstable Angina and Non–Q-Wave MI Patients	1578 (100)	1529 (100)		
Time point†				
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

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

† Evaluation time points are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

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)

	Dosing Regimen*			
Indication	**Lovenox** 1 mg/kg q12h subcutaneously n (%)	**Heparin** aPTT Adjusted Intravenous Therapy n (%)	**Reduction** (%)	**p Value**
All Treated Unstable Angina and Non–Q-Wave MI Patients	1578 (100)	1529 (100)		
Time point†				
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

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

† Evaluation time points are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

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

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

14.6 Treatment of Acute ST-Segment Elevation Myocardial Infarction

In a multicenter, double-blind, double-dummy, parallel-group study, patients with acute ST-segment elevation myocardial infarction (STEMI) who were to be hospitalized within 6 hours of onset and were eligible to receive fibrinolytic therapy were randomized in a 1:1 ratio to receive either Lovenox or unfractionated heparin.

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

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

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

Among 20,479 patients in the ITT population, the mean age was 60 years, and 76% were male. Racial distribution was: 87% Caucasian, 9.8% Asian, 0.2% Black, and 2.8% other. Medical history included previous MI (13%), hypertension (44%), diabetes (15%) and angiographic evidence of CAD (5%). Concomitant medication included aspirin (95%), beta-blockers (86%), ACE inhibitors (78%), statins (70%) and clopidogrel (27%). The MI at entry was anterior in 43%, non-anterior in 56%, and both in 1%.

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

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

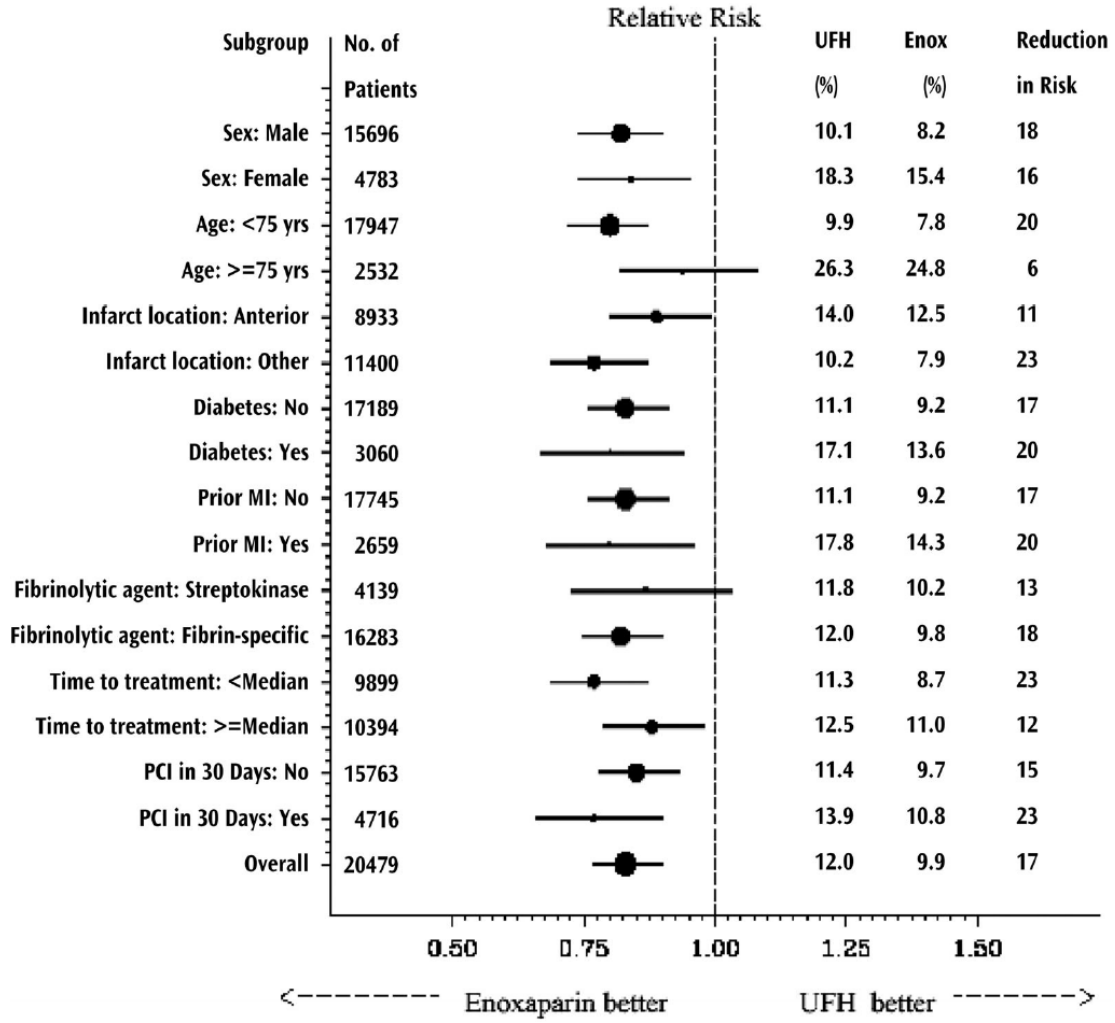
Table 25: Efficacy of Lovenox in the Treatment of Acute ST-Segment Elevation Myocardial Infarction

	Enoxaparin (N=10,256)	**UFH (N=10,223)**	**Relative Risk (95% CI)**	**P Value**
Outcome at 48 hours	n (%)	n (%)		
Death or Myocardial Re-infarction	478 (4.7)	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.

The beneficial effect of enoxaparin on the primary endpoint 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.

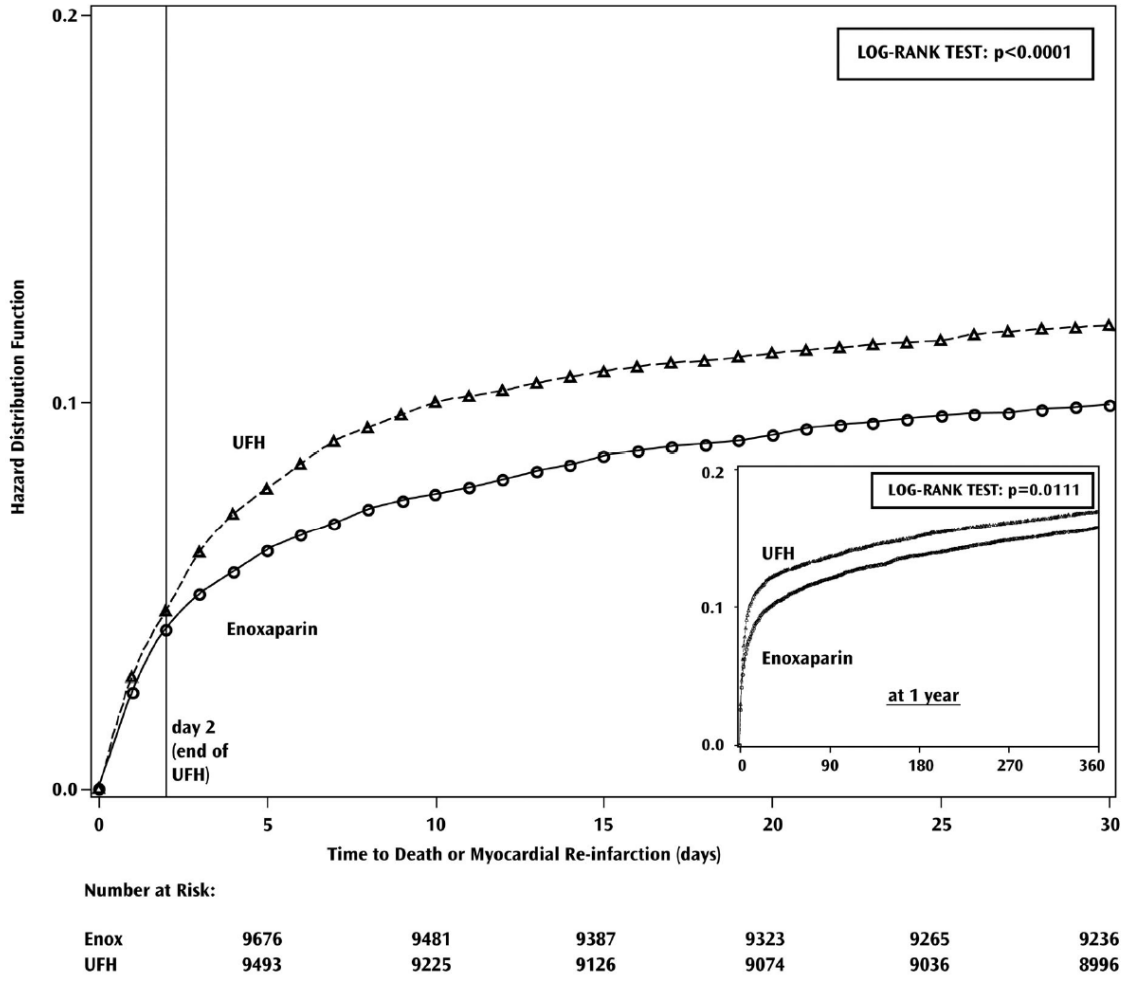
Figure 1: Relative Risks of and Absolute Event Rates for the Primary Endpoint at 30 Days in Various Subgroups*



* The primary efficacy endpoint 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% 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 endpoint observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2).

Figure 2: Kaplan-Meier Plot – Death or Myocardial Re-infarction at 30 Days – ITT Population



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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Lovenox is available in two concentrations (see Tables 26 and 27).

Table 26: 100 mg/mL Concentration

Dosage Unit/Strength*	Anti-Xa Activity†	Package Size (per carton)	Label Color	NDC # 0075-
Prefilled Syringes‡				
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 Syringes‡				
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 Vial§				
300 mg/3 mL	30,000 IU	1 vial	Red	0626-03

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

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

‡ Each Lovenox prefilled syringe is for single, one-time use only and is affixed with a 27 gauge × 1/2-inch needle.

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

Table 27: 150 mg/mL Concentration

Dosage Unit/Strength*	Anti-Xa Activity†	Package Size (per carton)	Syringe Label Color	NDC # 0075-
Graduated Prefilled Syringes‡				
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

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

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

‡ Each Lovenox graduated prefilled syringe is for single, one-time use only and is affixed with a 27 gauge × 1/2-inch needle.

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

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

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs, platelet inhibitors, or other anticoagulants, advise them to watch for signs and symptoms of spinal or epidural hematoma, such as tingling, numbness (especially in the lower limbs) and muscular weakness. Instruct the patient to seek immediate medical attention if any of these symptoms occur.

Additionally, the use of aspirin and other NSAIDs may enhance the risk of hemorrhage. When possible, discontinue their use prior to Lovenox therapy. Monitor the patient's clinical and laboratory status if coadministration is essential *[see Drug Interactions (7)]*.

Inform patients:

- of the instructions for injecting Lovenox if they continue Lovenox therapy after discharge from the hospital.
- that it may take them longer than usual to stop bleeding.
- that they may bruise and/or bleed more easily when they use Lovenox.
- that they should report any unusual bleeding, bruising, or signs of thrombocytopenia (such as a rash of dark red spots under the skin) to their physician *[see Warnings and Precautions (5.1, 5.5)]*.
- that risks are associated with the use of benzyl alcohol, a preservative in Lovenox multi-dose vials, in neonates, infants, and pregnant women.
- to tell their physicians and dentists they are taking Lovenox and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken *[see Warnings and Precautions (5.3)]*.
- to tell their physicians and dentists of all medications they are taking, including those obtained without a prescription, such as aspirin or other NSAIDs *[see Drug Interactions (7)]*.

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