Clinical Insights into

Enoxaparin Versus Unfractionated Heparin With Fibrinolysis for ST-elevation Myocardial Infarction


With a managed care analysis of the article by Steven R. Peskin, MD, MBA
The ExTRACT study (Antman 2006) summarized in this Clinical Brief provides clinical evidence for optimal management of ST-elevated myocardial infarction (STEMI). The investigators sought to determine if use of Lovenox® (enoxaparin sodium injection), a low molecular weight heparin (LMWH), provided any benefit over unfractionated heparin (UFH) in patients given fibrinolysis.

Study results found that for patients treated with fibrinolysis for STEMI, there was a significant benefit in the enoxaparin group compared to the UFH group at 30 days. Regardless of the fibrinolytic used, the patient’s age, or the location of the infarct, those who were given enoxaparin showed a reduction in ischemic outcomes according to a range of endpoints.

Although differentiation among forms of LMWH was not evaluated in the ExTRACT study, research shows that not all anti-coagulant therapeutic options are equal. The importance of not interchanging LMWHs was reaffirmed in a recently published study in Circulation, which stressed that these agents should be evaluated individually, rather than as a class, because of differences in the manufacturing process, molecular weight distribution, and other important distinctions (Antman 2008, Nightingale 1993).

The Antman (2006) article points out the advantages of enoxaparin within the context of STEMI. For formulary decision makers and clinical executives focused on optimizing improved clinical outcomes, the real world postmarketing data for enoxaparin is compelling. It is important to remember that enoxaparin has a variety of indications, more than 15 years of usage in the United States, and is used by more than 100 million people worldwide (data on file, sanofi-aventis). Physicians and other health care providers have extensive experience with enoxaparin. This familiarity may translate into greater consistency of use and quality of care.

The clinical findings summarized in this Clinical Brief suggest an opportunity for improved patient outcomes.

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

References
Data on file. sanofi-aventis, Bridgewater, N.J.
Nightingale SL. From the Food and Drug Administration. JAMA. 1993;270:1672.

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Dr. Peskin received a fee from sanofi-aventis U.S. LLC for his participation in this project.

Please refer to important safety information opposite page 6.
Study Highlights

TITLE

OBJECTIVE
Anticoagulation therapy with unfractionated heparin (UFH) often is used as an adjunct to fibrinolysis in patients with ST-elevation myocardial infarction (STEMI). This study compared Lovenox® (enoxaparin sodium injection), a low-molecular-weight heparin (LMWH), with UFH for this purpose.

STUDY PARAMETERS
This was a randomized, double-blind, double-dummy study that enrolled patients (n=20,506) with STEMI to be treated with fibrinolysis. Patients were randomly assigned to receive Lovenox throughout the index hospitalization, or weight-based UFH for at least 48 hours. Death or nonfatal MI through 30 days was the primary efficacy endpoint of the study.

RESULTS
Lovenox reduced the incidence of the primary efficacy endpoint compared with UFH (9.9% vs. 12.0%, respectively; relative risk reduction [RRR]=17%; *P*<.001). Nonfatal reinfarction occurred in 4.5% of patients in the UFH group and 3.0% in the Lovenox group (RRR=33%; *P*<.001). The composite of death, nonfatal reinfarction, or urgent revascularization occurred less often with Lovenox than UFH (11.7% vs. 14.5%; *P*<.001). Major bleeding (nonfatal, non-intracranial) occurred more often with Lovenox than UFH (2.1% vs. 1.4%; *P*<.001), but the composite of death, nonfatal reinfarction, or nonfatal intracranial hemorrhage (ICH) occurred less often with Lovenox than UFH (10.1% vs. 12.2%; *P*<.001), indicating a net clinical benefit in favor of Lovenox.

CONCLUSION
For patients being treated with fibrinolysis for STEMI, Lovenox throughout the index hospitalization is superior to treatment with UFH for at least 48 hours, and although it is associated with an increase in major bleeding episodes, the net clinical benefit of Lovenox compared to UFH is positive.
In choosing between fibrinolytic therapy and PCI, there is an easy bottom line: if PCI is readily available, it is the reperfusion therapy of choice. However, there are many cases in which PCI is not readily available and fibrinolytic therapy is a safe and effective alternative. In fact, the earlier patients can receive fibrinolytic therapy, the more likely they are to benefit from it. Guidelines from the ACC/AHA state that the standard target for “door-to-balloon” time (arrival at ED to catheterization lab with access established) for direct PCI should be no longer than 90 minutes. For fibrinolytic therapy, the lytic agent should be ready to inject (“door-to-needle” time) within 30 minutes of arriving at the ED.1

What was the objective of this study?
In the “lytic era,” the anticoagulant most commonly used with fibrinolysis has been UFH. The objective of the ExTRACT study2 was to determine whether Lovenox® (enoxaparin sodium injection) confers any benefit over UFH. The ASSENT-3 study gave researchers reason to believe that STEMI patients receiving fibrinolysis might derive some benefit from Lovenox over UFH.3 There are basic pharmacologic advantages of Lovenox over UFH, including a longer half-life, greater bioavailability, and more predictable activity. Lovenox can be dosed subcutaneously (SC) or given IV and monitoring of its effect generally is not necessary except in special circumstances. This is in contradistinction to the necessary ongoing monitoring with dose adjustment when using UFH. Activated partial thromboplastin time (APTT) is measured every 4 to 8 hours until the patient is stabilized, and then is checked daily thereafter.

Can you describe the design of this study including the inclusion criteria and study protocol?
This was a very well-designed, “double-blind, double-dummy,” international study with 20,506 patients who met the clinical and ECG criteria for STEMI. To be eligible, the clinical decision that the patient would be treated with fibrinolytic therapy and not direct PCI had already been made. The choice of fibrinolytic therapy was at the discretion of the treating physician. The dose used for UFH was a bolus of 60 U/kg (up to 4000 U), after which 12 U/kg (up to 1000 U)/hour were administered and patients were monitored to maintain APTT between 1.5 and 2.0 times control. These patients stayed on heparin for a minimum of 48 hours. Dosing of Lovenox was dependent upon patient age and renal status; patients younger than 75 received a 30-mg weight-independent bolus, then 10 to 15 minutes later received 1 mg/kg of Lovenox SC. The SC dose was repeated every 12 hours throughout their hospitalization. Patients 75 years or older did not get the bolus, and the SC dose was adjusted to .75 mg/kg, again every 12 hours.

What are the options, both pharmacological and mechanical, for reperfusion therapy in STEMI patients?
Reperfusion can be achieved in 2 basic ways: pharmacologic, with a fibrinolytic agent that is given intravenously (IV) to dissolve the clot in the coronary artery, or mechanical, by “direct” or “primary” percutaneous coronary intervention (PCI), performed in the cardiac catheterization lab. Fibrinolytic therapy is the more common type of STEMI reperfusion therapy in the US and worldwide, and, in the absence of the availability of rapid and expert primary PCI, is the standard-of-care management for patients with STEMI. Contraindications to fibrinolytic therapy are based on bleeding risk and hemodynamic stability. All fibrinolytic agents work by breaking down the thrombin and fibrin inside the platelet aggregates at the site of obstruction. Fibrin-specific lytic agents (reteplase, alteplase, and tenecteplase) are preferred in the US, while streptokinase is used less often, although its use worldwide remains relatively common. An anticoagulant is necessary to prevent ongoing coagulation in the affected area. Additionally, for a period of time after clot dissolution, patients remain in a hypercoagulable state because of the physiologic condition that caused the STEMI and because thrombogenic factors are released when fibrin and thrombin are dissolved. It is common to use anticoagulation with fibrin-specific fibrinolytics, but in the past, not with streptokinase.

What is STEMI and what does it mean for patients in terms of prognosis and risk for recurrent MI?
ST-segment elevation MI—the classic “heart attack”—reflects transmural injury and does not always present with typical symptoms. The symptoms usually include chest pain, but occasionally patients may have jaw or arm pain, shortness of breath, or nausea without chest pain. By definition, all STEMI patients have abnormal electrocardiograms (ECG), showing either ST-segment elevation in contiguous leads, or a new (or presumed new) left bundle branch block on the ECG, which indicates that the patient is at significant risk of short-term mortality. There also is the likelihood of recurrence due to the atherosclerotic burden that caused the primary event. About half a million cases of STEMI per year are recorded.1 The prognosis for STEMI depends on a number of factors including patient age and the location of the infarct. Generally, patients suffering from anterior wall infarcts have a poorer prognosis.

In the cardiac catheterization lab, 48 hours. Dosing of Lovenox was dependent upon patient age and renal status; patients younger than 75 received a 30-mg weight-independent bolus, then 10 to 15 minutes later received 1 mg/kg of Lovenox SC. The SC dose was repeated every 12 hours throughout their hospitalization. Patients 75 years or older did not get the bolus, and the SC dose was adjusted to .75 mg/kg, again every 12 hours. Patients with creatinine clearance <30 mL/min received only 1 daily dose of Lovenox instead of two.
In the past, it had not been recommended that anticoagulation be given with streptokinase. Another question to be answered in this study was whether adding anticoagulation to streptokinase improves outcomes without unacceptably increasing bleeding risk. **What was the primary efficacy endpoint and what were the results?**

The primary endpoint of the study was death or nonfatal recurrent MI within 30 days. At 30 days, there was a significant benefit in the Lovenox® (enoxaparin sodium injection) group compared with UFH; as shown in Figure 1, 9.9% of patients in the Lovenox group died or suffered a nonfatal recurrent MI versus 12.0% of patients treated with UFH (RRR=17%; P<.001). Similar results were observed at day 8, where 7.2% of patients satisfied the primary endpoint in the Lovenox arm versus 9.3% in the UFH group (RRR=13%; P<.001), but even at 48 hours, Lovenox was statistically superior to UFH in the reduction of nonfatal MI (P<.001) as well as with the combined endpoint of death, nonfatal MI, or urgent revascularization (P<.001).

**What was the secondary endpoint of this study and what was the result?**

The major secondary endpoint was a composite of death, nonfatal recurrent MI, or urgent revascularization within 30 days. Urgent revascularization measures the number of episodes of recurrent myocardial ischemia that required the clinician to perform PCI or CABG. On this endpoint, a significant benefit again was seen with Lovenox over UFH (11.7% vs. 14.5%, P<.001, RRR=19%). It did not take long for these curves to diverge (they had already separated, favoring Lovenox, at 48 hours), and they continued to improve over time. **What is the basis and results of the “net clinical benefit” endpoints?**

Another objective of this study was to evaluate the safety performance of the two arms of therapy. The concept of net clinical benefit combines efficacy and safety outcomes to give a clearer picture of the effect of using the therapy than is shown by focusing only on efficacy results. The first of the net clinical benefit measures tested was death, nonfatal MI, or nonfatal disabling stroke. Disabling stroke is a very important safety outcome, and a reason that many physicians may hesitate when using fibrinolytic therapy for STEMI. In the group treated with Lovenox, there was a statistically significant reduction in this measure versus patients treated with UFH (18% RRR). The second net clinical benefit measure was broader and included nonfatal major bleeding (including nonfatal disabling stroke as well as other major bleeding episodes). Again, a significant benefit was observed in the group treated with Lovenox versus UFH (RRR=14%). Finally, the third measure looked at nonfatal intracranial hemorrhage, which is the type of stroke that is most worrisome in patients receiving fibrinolysis; again, a significant benefit was seen with Lovenox (RRR=17%).

**What were the results in terms of safety?**

There was more nonfatal major bleeding in the patients who received Lovenox. Although the difference was significant because of the size of the study, the actual numbers were small. Out of over 20,000 patients, there was a 45-patient difference between the two study arms. Much more reassuring is the fact that at 48 hours, 8 days, and 30 days, there was no significant difference between the treatment groups in terms of ICH. There is an increase in bleeding with Lovenox at all time points, but I believe that this risk is offset by the efficacy advantages. **Why did the researchers stop UFH after 48 hours but continue Lovenox? Did it affect the outcomes?**

The reason that 48 hours was established as the minimum time for UFH is that there are no data showing that more than 48 hours’ therapy is helpful in patients with STEMI who received a fibrinolytic. When we look at the data, there was already a separation of the efficacy endpoints at 48 hours. There is no reason to believe, based on previous data, that any additional benefit with UFH would be seen beyond 48 hours, and we would in fact expect bleeding complications to be more common with UFH had it been continued. **Did the researchers look at different patient subgroups? What were the findings there?**

The researchers looked at a number of prespecified subgroups. There was not a single endpoint for which a benefit of Lovenox over UFH was not apparent. This is very reassuring. One interesting subgroup was the 23% of patients who proceeded to PCI within 30 days; these were generally elective, given that only 2.8% required PCI as rescue therapy. Many were still on Lovenox, because the PCI was often done during their index hospitalization. In contemporary US practice, where it is common for patients who have undergone fibrinolysis to have elective PCI, this study shows that Lovenox provides a durable benefit over UFH. Please remember it’s important to interpret subgroup analyses with caution. **Based on the results of this study, what role should Lovenox play for the hospital management of patients following STEMI?**

Emergency physicians and cardiologists should know that, despite the recent emphasis on primary PCI, fibrinolysis is an effective treatment option for STEMI patients (unless specifically contraindicated), and should not be considered a second-class therapy. ExTRACT demonstrated that in this patient population, Lovenox was superior to UFH.

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Please see important safety information on back page. Please see accompanying full prescribing information for LOVENOX, including boxed WARNING.
Important Safety Information

WARNING: SPINAL/EPIDURAL HEMATOMAS

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

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

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

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

- **LOVENOX®** (enoxaparin sodium injection) cannot be used interchangeably with other low-molecular-weight heparins or unfractionated heparin (UFH), as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage

- As with other anticoagulants, use with extreme caution in patients with conditions that increase the risk of hemorrhage. Dosage adjustment is recommended in patients with severe renal impairment. Unless otherwise indicated, agents that may affect hemostasis should be discontinued prior to LOVENOX® therapy. Bleeding can occur at any site during LOVENOX® therapy. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site. (See WARNINGS and PRECAUTIONS)

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

- Thrombocytopenia can occur with LOVENOX®. In patients with a history of heparin-induced thrombocytopenia (HIT), LOVENOX® should be used with extreme caution. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, LOVENOX® should be discontinued. Cases of HIT have been observed in clinical practice. (See WARNINGS and PRECAUTIONS)

- The use of LOVENOX® has not been adequately studied for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves. (See WARNINGS and PRECAUTIONS)

- LOVENOX® is contraindicated in patients with hypersensitivity to enoxaparin sodium, heparin, or pork products, and in patients with active major bleeding

For more information, contact your local sanofi-aventis Representative or call sanofi-aventis Medical Information Services at 1-800-633-1610.

Please see accompanying full prescribing information, including boxed WARNING.

Additional Resources

**Lovenox Healthcare Professionals Website:**
http://www.lovenox.com/hcp/default.aspx

**References**


This program was developed in conjunction with and funded by sanofi-aventis U.S. LLC.

Dr. Charles Pollack received a fee from sanofi-aventis U.S. LLC for his participation in this project.

For additional clinical study summaries, visit www.clinicalimpressions.com

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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)

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

DOSAGE AND ADMINISTRATION
Indication Standard Regimen 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

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.

Indications and Usage
- 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
- 150 mg/mL concentration (3.2):
  - Graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL
- 100 mg/mL concentration (3.1):
  - Graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL
- Multiple-dose vials: 300 mg/3 mL

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

Drug Interactions
- Avoid concomitant use of drugs affecting coagulation, nonsteroidal anti-inflammatory drugs, platelet inhibitors, anticoagulants, and other agents which may enhance hemorrhage risk (5.5, 7)

Use in Specific Populations
- Pregnancy (8.1)
- Nursing Mothers (8.3)
- Pediatric Use (8.4)
- Geriatric Use (8.5)
- Patients with Mechanical Prosthetic Heart Valves (8.6)
- Renal Impairment (8.7)
- Hepatic Impairment (8.8)
- Low-Weight Patients (8.9)

Overdosage

CLINICAL STUDIES
- Prophylaxis of Deep Vein Thrombosis (DVT) Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications (14.1)
- Prophylaxis of Deep Vein Thrombosis (DVT) Following Hip or Knee Replacement Surgery (14.2)
- Prophylaxis of Deep Vein Thrombosis (DVT) in Medical Patients with Severely Restricted Mobility During Acute Illness (14.3)
- Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE) (14.4)
- Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (14.5)
- Treatment of acute ST-segment elevation myocardial infarction (STEMI) (14.6)

How Supplied/Storage and Handling

RECENT MAJOR CHANGES

Lovenox® (enoxaparin sodium injection) for subcutaneous and intravenous use

Full Prescribing Information: Contents

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

INDICATIONS AND USAGE
- 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)

INDICATIONS AND USAGE

1 INDICATIONS AND USAGE
1.1 Prophylaxis of Deep Vein Thrombosis
1.2 Treatment of Acute Deep Vein Thrombosis
1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial Infarction
1.4 Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)

2 DOSAGE AND ADMINISTRATION
2.1 Adult Dosage
2.2 Renal Impairment
2.3 Geriatric patients with acute ST-segment Elevation Myocardial Infarction
2.4 Administration

3 DOSAGE FORMS AND STRENGTHS
3.1 100 mg per mL
3.2 150 mg per mL

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
5.1 Increased Risk of Hemorrhage
5.2 Percutaneous Coronary Revascularization Procedures
5.3 Use of Lovenox with Concomitant Medical Conditions
5.4 History of Heparin-induced Thrombocytopenia
5.5 Thrombocytopenia
5.6 Interchangeability with Other Heparins
5.7 Pregnant Women with Mechanical Prosthetic Heart Valves
5.8 Benzyl Alcohol
5.9 Laboratory Tests

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

9.7 Laboratory Tests

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology

14 CLINICAL STUDIES
14.1 Prophylaxis of Deep Vein Thrombosis (DVT) Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications
14.2 Prophylaxis of Deep Vein Thrombosis (DVT) Following Hip or Knee Replacement Surgery
14.3 Prophylaxis of Deep Vein Thrombosis (DVT) in Medical Patients with Severely Restricted Mobility During Acute Illness
14.4 Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE)
14.5 Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction
14.6 Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)

15 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Revised: October 2007

*Sections or subsections omitted from the full prescribing information are not listed
WARNING: SPINAL / EPIDURAL HEMATOMAS

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

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

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

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

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Deep Vein Thrombosis

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

• in patients undergoing abdominal surgery who are at risk for thromboembolic complications [see Clinical Studies (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 surgery, immobilization, or hospitalization.
• in patients after major orthopedic surgery requiring inpatient and outpatient treatment.
• the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

1.2 Treatment of Acute Deep Vein Thrombosis

Lovenox is indicated for:

• the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin therapy.
• the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered under medical management.

1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial Infarction

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

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

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

2 DOSAGE AND ADMINISTRATION

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

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

Lovenox is not intended for intramuscular administration.

2.1 Adult Dosage

Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox is 40 mg once a day administered SC, with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 14 days administration has been administered in clinical trials.

Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox is 30 mg every 12 hours administered SC, with the initial dose given 2 hours prior to surgery. For hip replacement surgery, a dose of 40 mg once a day SC, given initially 12 (+3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, it is recommended that continued prophylaxis with Lovenox 40 mg once a day is administered by SC injection for 3 weeks. The usual duration of administration is 7 to 10 days; up to 14 days administration has been administered in clinical trials.

Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to immobility or mobility during acute illness, the recommended dose of Lovenox is 40 mg once a day administered SC by injec-

2.2 Geriatric patients with acute ST-segment Myocardial Infarction

Once daily). Treatment with Lovenox should be prescribed for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox has been administered in clinical trials. [See Warnings and Precautions (5.2) and Clinical Studies (14.5)].

2.3 Geriatric patients with acute ST-segment Myocardial Infarction

In patients with acute ST-segment Elevation Myocardial Infarction, the recommended dose of Lovenox is a single IV bolus of 30 mg plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours (maximum 180 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining doses). Dosage adjustments are recommended in patients ≥75 years of age [see Dosage and Administration (2.2)].

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

For patients managed with Percutaneous Coronary Intervention (PCI): If the last Lovenox administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last Lovenox SC administration was given more than 8 hours but less than 12 hours before balloon inflation, an IV bolus of 0.3 mg/kg of Lovenox should be administered [see Warnings and Precautions (5.2)].

2.4 Renal Impairment

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all patients with severe renal impairment (creatinine clearance <30 mL/min) should be carefully monitored.

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 (8.6) and Clinical Pharmacology (12.3)].

Table 1

<table>
<thead>
<tr>
<th>Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance &lt;30mL/minute)</th>
<th>Indication</th>
<th>Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis in abdominal surgery</td>
<td>30 mg administered SC once daily</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis in hip or knee replacement surgery</td>
<td>30 mg administered SC once daily</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis in medical patients during acute illness</td>
<td>30 mg administered SC once daily</td>
<td></td>
</tr>
<tr>
<td>Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium</td>
<td>1 mg/kg administered SC once daily</td>
<td></td>
</tr>
<tr>
<td>Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium</td>
<td>1 mg/kg administered SC once daily</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin</td>
<td>1 mg/kg administered SC once daily</td>
<td></td>
</tr>
<tr>
<td>Treatment of acute ST-segment Elevation Myocardial Infarction in patients &lt;75 years of age</td>
<td>30-mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC once daily</td>
<td></td>
</tr>
<tr>
<td>Treatment of acute ST-segment Elevation Myocardial Infarction in geriatric patients ≥75 years of age</td>
<td>1 mg/kg administered SC once daily (no initial bolus)</td>
<td></td>
</tr>
</tbody>
</table>
| 2.5 Multiple-dose Vials | For treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), multiple-dose vials to assure withdrawal of the appropriate volume of drug.

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

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.

Subcutaneous injection Technique: Patients should be shown how to inject 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 posterior lateral abdominal wall areas. The needle 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.
Lovenox prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

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.

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

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

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).

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

NOTE:
- 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.

3 DOSE FORMS AND STRENGTHS
Lovenox is available in two concentrations:

3.1 100 mg per mL
- Prefilled Syringes
- Graduated Prefilled Syringes
- Multiple-Dose Vials
3.2 150 mg per mL
- Graduated Prefilled Syringes

4 CONTRAINDICATIONS
- Active major bleeding.
- Thrombocytopenia associated with a positive in vitro test for anti-platelet antibody in the presence of enoxaparin sodium.
- Known hypersensitivity to enoxaparin sodium (e.g., pruritus, urticaria, anaphylactic/anaphylactoid reactions) [see Adverse Reactions (6.2)].
- Known hypersensitivity to heparin or pork products.
- Known hypersensitivity to benzyl alcohol (which is in only the multi-dose formulation of Lovenox).

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

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

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal. Bleeding can occur at any site during therapy with Lovenox. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

5.2 Percutaneous Coronary Revascularization Procedures
To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between Lovenox doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC Lovenox. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation [see Dosage and Administration (2.1)].

5.3 Use of Lovenox with Concomitant Medical Conditions
Lovenox should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.

5.4 History of Heparin-induced Thrombocytopenia
Lovenox should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

5.5 Thrombocytopenia
Thrombocytopenia can occur with the administration of Lovenox. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given Lovenox, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials.

Platelet counts less than 50,000/mm³ occurred at a rate of 0.1% in patients given Lovenox, 0.7% in patients given placebo in clinical trials. Moderate thrombocytopenia of any degree should be monitored closely. If the platelet count falls in the presence of enoxaparin sodium.

5.6 Interchangeability with Other Heparins
Lovenox cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-ila activities, units, and dosage. Each of these medicines has its own instructions for use.

5.7 Pregnant Women with Mechanical Prosthetic Heart Valves
The use of Lovenox for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (9 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Xa levels, and adjusting of dosage may be needed [see Use in Specific Populations (8.6)].
5.8 Benzyl Alcohol

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

5.9 Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox activity and, therefore, unsuitable for monitoring. Anti-Factor Xa levels may be used to monitor the anticoagulant effect of Lovenox in patients with significant renal impairment. If during Lovenox therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox [see Clinical Pharmacology (12.2)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Hemorrhage

The incidence of major hemorrhagic complications during Lovenox treatment has been low. The following rate of major bleeding events has been reported during clinical trials with Lovenox Injection [see Tables 2 to 7].

Table 2

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Surgery</td>
<td>Lovenox 40 mg q.d. SC</td>
</tr>
<tr>
<td></td>
<td>Heparin 5000 U q8h SC</td>
</tr>
<tr>
<td>Colorectal Surgery</td>
<td>Lovenox n = 595</td>
</tr>
<tr>
<td></td>
<td>Heparin n = 580</td>
</tr>
<tr>
<td></td>
<td>(23%)</td>
</tr>
<tr>
<td></td>
<td>(16%)</td>
</tr>
</tbody>
</table>

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

Table 3

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

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

Table 5

<table>
<thead>
<tr>
<th>Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Lovenox</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td>Treatment of DVT and PE</td>
<td>5.9 mg/kg q.d. SC</td>
</tr>
<tr>
<td></td>
<td>n = 208</td>
</tr>
<tr>
<td></td>
<td>n = 569</td>
</tr>
<tr>
<td></td>
<td>(2%)</td>
</tr>
<tr>
<td></td>
<td>(2%)</td>
</tr>
</tbody>
</table>

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

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

Table 6

<table>
<thead>
<tr>
<th>Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Lovenox</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg q12h SC</td>
</tr>
<tr>
<td>Unstable Angina and Non-Q-Wave MI†</td>
<td>n = 1578</td>
</tr>
<tr>
<td></td>
<td>n = 1529</td>
</tr>
<tr>
<td></td>
<td>(17%)</td>
</tr>
<tr>
<td></td>
<td>(18%)</td>
</tr>
</tbody>
</table>

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

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

Table 7

<table>
<thead>
<tr>
<th>Major Bleeding Episodes in acute ST-segment Elevation Myocardial Infarction</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Lovenox</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg q12h SC</td>
</tr>
<tr>
<td>acute ST-segment Elevation Myocardial Infarction</td>
<td>n = 10176</td>
</tr>
<tr>
<td>- Major bleeding (including ICH)†</td>
<td>n = 10151</td>
</tr>
<tr>
<td>- Intracranial hemorrhages (ICH)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>211 (2.1)</td>
</tr>
<tr>
<td></td>
<td>138 (1.4)</td>
</tr>
<tr>
<td></td>
<td>84 (0.8)</td>
</tr>
<tr>
<td></td>
<td>66 (0.7)</td>
</tr>
</tbody>
</table>

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

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.

Thrombocytopenia:

[See Warnings and Precautions (5.5)]

Table 8

<table>
<thead>
<tr>
<th>Major Bleeding Episodes in Medical Patients With Severe Local Morbidity During Acute Illness</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Lovenox</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td>1.5 mg/kg q.d. SC</td>
</tr>
<tr>
<td></td>
<td>n = 1228</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td>5000 U q8h SC</td>
</tr>
<tr>
<td></td>
<td>n = 1234</td>
</tr>
<tr>
<td></td>
<td>(6%)</td>
</tr>
<tr>
<td></td>
<td>(7%)</td>
</tr>
<tr>
<td></td>
<td>(7%)</td>
</tr>
</tbody>
</table>

1 Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intracranial, and intracranial hemorrhages were always considered major. No clinical events were noted.

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

Table 9

<table>
<thead>
<tr>
<th>Major Bleeding Episodes Occurring at ≥2% Incidence in Lovenox-Treated Patients Undergoing Abdominal or Colorectal Surgery</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Lovenox</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td>40 mg q.d. SC</td>
</tr>
<tr>
<td></td>
<td>5000 U q8h SC</td>
</tr>
<tr>
<td></td>
<td>n = 1228</td>
</tr>
<tr>
<td></td>
<td>n = 1234</td>
</tr>
<tr>
<td></td>
<td>(5%)</td>
</tr>
<tr>
<td></td>
<td>(6%)</td>
</tr>
</tbody>
</table>

1 Excluding unrelated adverse events.
Table 9

<table>
<thead>
<tr>
<th>Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients</th>
<th>Undergoing Hip or Knee Replacement Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td><strong>Lovenox</strong></td>
</tr>
<tr>
<td></td>
<td><strong>40 mg q.d. SC</strong></td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td><strong>Percent</strong></td>
</tr>
<tr>
<td>FEVER</td>
<td>40</td>
</tr>
<tr>
<td>INFECTION SITE PAIN</td>
<td>0</td>
</tr>
<tr>
<td>HEMORRHAGE</td>
<td>10</td>
</tr>
<tr>
<td>INFARCTION SITE PAIN</td>
<td>&lt;1</td>
</tr>
<tr>
<td>INTRAURAL EDEMA</td>
<td>5</td>
</tr>
</tbody>
</table>

1 Excluding unrelated adverse events.

Table 10

<table>
<thead>
<tr>
<th>Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Medical Patients</th>
<th>With Severely Restrictcd Mobility During Acute Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lovenox</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td></td>
<td><strong>40 mg q.d. SC</strong></td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td><strong>Percent</strong></td>
</tr>
<tr>
<td>ANEMIA</td>
<td>16</td>
</tr>
<tr>
<td>CONFUSION</td>
<td>2</td>
</tr>
<tr>
<td>DIARRHEA</td>
<td>2</td>
</tr>
<tr>
<td>HEMORRHAGE</td>
<td>&lt;1</td>
</tr>
<tr>
<td>INFECTION SITE PAIN</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Excluding unrelated and unlikely adverse events.

Table 11

<table>
<thead>
<tr>
<th>Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients</th>
<th>Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lovenox</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1.5 mg/kg q.d. SC</strong></td>
</tr>
<tr>
<td></td>
<td><strong>n = 298</strong></td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td><strong>Percent</strong></td>
</tr>
<tr>
<td>INJECTION SITE HEMORRHAGE</td>
<td>5</td>
</tr>
<tr>
<td>INJECTION SITE PAIN</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Excluding unrelated adverse events.

Table 12

<table>
<thead>
<tr>
<th>Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox-Treated Patients</th>
<th>With Unstable Angina or Non-Q-Wave Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lovenox</strong></td>
<td><strong>Heparin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1 mg/kg q12h SC</strong></td>
</tr>
<tr>
<td></td>
<td><strong>n = 1578</strong></td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td><strong>Percent</strong></td>
</tr>
<tr>
<td>ATRIAL FIBRILLATION</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Concentration</td>
<td>11 (0.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13 (0.9)</td>
</tr>
</tbody>
</table>

1 Excluding unrelated adverse events.

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, the only additional possibly related adverse reaction that occurred at a rate of at least 0.5% in the Lovenox group was thrombocytopenia (1.5%).

6.2 Post-Marketing Experience
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 post-operative 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.

7 DRUG INTERACTIONS
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 ketoroloc, trimethamine), dipryridamole, or sulfonpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring [see Warnings and Precautions (5.8)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Category B
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.

Fetal Risk Summary
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.

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 mL as a preservative [see Warnings and Precautions (5.8)].

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

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 routinely studied, pregnant women with moderate to severe 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 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 of use of other anticoagulants 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.

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 SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m²/day and 410 mg/m²/day, respectively. 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 this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox is administered to nursing women.

8.4 Pediatric Use
Safety and effectiveness of Lovenox in pediatric patients have not been established.
8.5 Geriatric Use
Pharmacokinetic trials were conducted using the 100 mg/ml formulation. Over 2000 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 with a dose of 1 mg/kg every 12 hours or 40 mg once a day. Patients with renal impairment who were aged ≥65 years were enrolled. 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 bleeding occurred 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 (5.7)].

8.6 Patients with Mechanical Prosthetic Heart Valves
The use of Lovenox has not been adequately studied for thromboprophylaxis in patients with mechanical heart valves. Limited clinical experience has not been adequately studied for therapeutic 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 thrombotic events did not result in maternal and fetal death. Inadequate data does not exist to determine the possibility of adequate anticoagulation complication 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)].

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)].

10 OVERDOSAGE
Accidental overdosage following administration of Lovenox may lead to hemorrhagic complications. In patients who are unlikely to be neutrophilized by the slowly IV administration 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 hypertension 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.
The volume of distribution of anti-Factor Xa activity is about 4.3 L. Placebo Heparin No pharmacokinetic interaction was observed between abdominal surgery patients at risk include those who are over 40 years of age, obese, and female rats at SC doses up to 20 mg/kg/day or 141 mg/m2/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m2).

13 Animal Toxicology
A single SC dose of 46-6 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

14 CLINICAL STUDIES
14.1 Prophylaxis of Deep Vein Thrombosis (DVT) 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 DVT or pulmonary embolism.
In a double-blind study, patients without clinical signs and symptoms of VTE disease were examined for clinical signs and symptoms of venous thromboembolic (VTE) disease. 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 SC 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 17

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>All Treated DVT</th>
<th>Total DVT</th>
<th>Proximal DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DVT</td>
<td>10 mg q.d. SC</td>
<td>191 (100)</td>
<td>208 (100)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Total DVT</td>
<td>30 mg q12h SC</td>
<td>191 (100)</td>
<td>208 (100)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Total DVT</td>
<td>40 mg q.d. SC</td>
<td>191 (100)</td>
<td>208 (100)</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>

1. $p$ value versus Lovenox 10 mg once a day = 0.0008
2. $p$ value versus Lovenox 40 mg once a day = 0.0168

### Table 18

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>All Treated DVT</th>
<th>Total DVT</th>
<th>Proximal DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovenox</td>
<td>30 mg q12h SC</td>
<td>40 (100)</td>
<td>40 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>q12h SC</td>
<td>40 (100)</td>
<td>40 (100)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

1. $p$ value versus placebo = 0.0001
2. CI = Confidence Interval
3. $p$ value versus placebo = 0.013
4. CI = Confidence Limit

### Table 19

<table>
<thead>
<tr>
<th>Indication</th>
<th>Post-Dischage Dosing Regimen</th>
<th>Lovenox</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DVT</td>
<td>40 mg q.d. SC</td>
<td>90 (100)</td>
<td>90 (100)</td>
</tr>
<tr>
<td>Total DVT</td>
<td>q12h SC</td>
<td>90 (100)</td>
<td>90 (100)</td>
</tr>
</tbody>
</table>

Efficacy of Lovenox in the 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 SC, initiated up to 12 hours prior to surgery for the prophylaxis of post-operative 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 SC 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 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 (DVT) 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 SC was compared to placebo in the prophylaxis of 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 anaphylactic 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 SC, Lovenox significantly reduced the incidence of DVT as compared to placebo. The efficacy data are provided below (see Table 20).

### Table 20

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Lovenox</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failure1</td>
<td>20 mg q.d. SC</td>
<td>351 (100)</td>
<td>360 (100)</td>
</tr>
<tr>
<td>Treatment Failure1</td>
<td>40 mg q.d. SC</td>
<td>362 (100)</td>
<td>362 (100)</td>
</tr>
</tbody>
</table>

1. Treatment failures during therapy, between Days 1 and 14.
2. VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
3. CI = Confidence Interval

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

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

In a multicenter, parallel group study, 900 patients with acute lower extremity DVT with or without PE were randomized to an inpatient [hospital] treatment of either (i) Lovenox 1.5 mg/kg once a day SC, (ii) Lovenox 1 mg/kg every 12 hours SC, or (iii) heparin IV 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 to maintain INR between 2.0 and 3.0) commencing with 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 targetedwarfarin INR was achieved. Both Lovenox and standard heparin therapy 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Lovenox</th>
<th>Lovenox</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DVT</td>
<td>1.5 mg/kg q.d. SC</td>
<td>290 (100)</td>
<td>154 (100)</td>
<td>290 (100)</td>
</tr>
<tr>
<td>Total DVT</td>
<td>1 mg/kg q12h SC</td>
<td>290 (100)</td>
<td>154 (100)</td>
<td>290 (100)</td>
</tr>
</tbody>
</table>

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 DVT were: Lovenox once a day versus heparin (-3.0 to 3.5) Lovenox every 12 hours versus heparin (-4.2 to 1.7).
4. 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 co-morbid conditions or potential for non-compliance and inability to attend follow-up visits as an
Efficacy of Lovenox in the 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 SC or heparin IV bolus (5000 U) followed by a continuous infusion to achieve an aPTT of 60 to 85 seconds. A total of 3171 patients were enrolled in the study, and 3107 patients remained in age from 25-94 years (mean 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. Eighty percent of patients were treated with aspirin for a minimum of 30 days. 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 administration was less than 8 hours before balloon inflation, IV bolus of 0.3 mg/kg enoxaparin if the last administration was more than 8 hours before balloon inflation.

All patients were treated with aspirin for a minimum of 30 days. Eighty percent of percent patients received a fibrin-specific agent (19% tenecteplase, 5% reteplase and 35% alteplase) and 20% received streptokinase.

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

Table 22

<table>
<thead>
<tr>
<th>Indication</th>
<th>Lovenox</th>
<th>Enoxaparin</th>
<th>Timepoint</th>
<th>n (%)</th>
<th>n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated DVT Patients</td>
<td>247 (100)</td>
<td>254 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT Only</td>
<td>13 (5.3)</td>
<td>14 (5.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>10 (4.0)</td>
<td>12 (4.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 All patients were also treated with warfarin sodium commencing on the evening of the second day of Lovenox Injection or standard heparin therapy. 2 VTE = venous thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]). 3 The 95% Confidence Intervals for the treatment difference for total VTE was: Lovenox versus heparin (-5.6 to 2.7).

Table 23

<table>
<thead>
<tr>
<th>Indication</th>
<th>Lovenox 1 mg/kg q12h SC</th>
<th>Heparin</th>
<th>Reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated unstable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>EPTI Adjusted IV Therapy n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=10,256</td>
<td>N=10,223</td>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timepoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 Hours</td>
<td>96 (6.1)</td>
<td>112 (7.3)</td>
<td>1.2</td>
<td>0.120</td>
</tr>
<tr>
<td>14 Days</td>
<td>261 (18.3)</td>
<td>305 (19.9)</td>
<td>3.3</td>
<td>0.0017</td>
</tr>
<tr>
<td>30 Days</td>
<td>513 (19.8)</td>
<td>358 (22.4)</td>
<td>3.6</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

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).

Table 24

<table>
<thead>
<tr>
<th>Indication</th>
<th>Lovenox 1 mg/kg q12h SC</th>
<th>Heparin</th>
<th>Reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated unstable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>EPTI Adjusted IV Therapy n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=10,256</td>
<td>N=10,223</td>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timepoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 Hours</td>
<td>16 (1.0)</td>
<td>20 (1.3)</td>
<td>0.3</td>
<td>0.126</td>
</tr>
<tr>
<td>14 Days</td>
<td>76 (4.8)</td>
<td>93 (6.1)</td>
<td>1.3</td>
<td>0.115</td>
</tr>
<tr>
<td>30 Days</td>
<td>96 (6.1)</td>
<td>118 (7.7)</td>
<td>1.6</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

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).

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).

Table 25

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lovenox</th>
<th>Enoxaparin</th>
<th>Relative Risk (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint (Death or Myocardial Re-infarction)</td>
<td>1017 (9.9)</td>
<td>1223 (12.0)</td>
<td>0.83 (0.77 to 0.90)</td>
<td>0.000003</td>
</tr>
<tr>
<td>Death</td>
<td>708 (6.9)</td>
<td>765 (7.5)</td>
<td>0.92 (0.84 to 1.02)</td>
<td>0.11</td>
</tr>
<tr>
<td>Myocardial Re-infarction</td>
<td>352 (3.4)</td>
<td>508 (5.0)</td>
<td>0.69 (0.51 to 0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>213 (2.1)</td>
<td>286 (2.8)</td>
<td>0.74 (0.62 to 0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or Myocardial Re-infarction</td>
<td>1199 (11.7)</td>
<td>1479 (14.5)</td>
<td>0.81 (0.75 to 0.87)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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 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. 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. 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Table 26

<table>
<thead>
<tr>
<th>Dosage Unit / Strength</th>
<th>Anti-Xa Activity</th>
<th>Package Size (per carton)</th>
<th>Label Color</th>
<th>NDC #</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg / 0.3 mL</td>
<td>3000 IU</td>
<td>10 syringes</td>
<td>Medium Blue</td>
<td>0624-30</td>
</tr>
<tr>
<td>40 mg / 0.4 mL</td>
<td>4000 IU</td>
<td>10 syringes</td>
<td>Yellow</td>
<td>0620-40</td>
</tr>
</tbody>
</table>

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 2.3% in the enoxaparin group and 4.4% 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%).