

Rx only
These highlights do not include all the information needed to use Enoxaparin Sodium Injection safely and effectively. See full prescribing information for Enoxaparin Sodium Injection.
Enoxaparin Sodium Injection for subcutaneous and intravenous use
Initial U.S. Approval: 1993

WARNING: SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning.
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 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 Enoxaparin Sodium Injection 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 [see Warnings and Precautions (5.1) and Drug Interactions (7)].

RECENT MAJOR CHANGES
Warnings and Precautions (5.1) 11/13
Warnings and Precautions (5.1) 11/13

INDICATIONS AND USAGE
Enoxaparin Sodium Injection 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
• 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)

DOSE AND ADMINISTRATION

Indication	Dose
DVT prophylaxis in abdominal surgery	40 mg SC once daily
DVT prophylaxis in knee replacement surgery	30 mg SC every 12 hours
DVT prophylaxis in hip replacement surgery	30 mg SC every 12 hours or 40 mg SC once daily
DVT prophylaxis in medical patients	40 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*

(continued)

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING - SPINAL/EPIDURAL HEMATOMAS

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FULL PRESCRIBING INFORMATION
WARNING: SPINAL/EPIDURAL HEMATOMAS
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 Enoxaparin Sodium Injection 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.
Consider the benefits and risks 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
Enoxaparin Sodium Injection is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
• 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, and during and following knee replacement surgery.
• in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.
1.2 Treatment of Acute Deep Vein Thrombosis
Enoxaparin Sodium Injection is indicated for:
• the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium.
• the outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium.
1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial Infarction
Enoxaparin Sodium Injection 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
Enoxaparin Sodium Injection, when administered concurrently with aspirin, has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction (STEMI) receiving thrombolysis and being managed medically or with percutaneous coronary intervention (PCI).

2. DOSAGE AND ADMINISTRATION
All patients should receive a bleeding disorder before administration of Enoxaparin Sodium Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Enoxaparin Sodium Injection activity, routine monitoring of coagulation parameters is not required [see Warnings and Precautions (5.9)]. For subcutaneous use, Enoxaparin Sodium Injection should not be mixed with other injections or infusions.
For intravenous use (i.e., for treatment of acute STEMI), Enoxaparin Sodium Injection can be mixed with normal saline solution (0.9% or 5% dextrose in water).
2.1 Adult Dosage
Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Enoxaparin Sodium Injection is 40 mg once a day administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 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 Enoxaparin Sodium Injection is 30 mg every 12 hours administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of 40 mg once a day SC is given initially 12 (2,3) 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 Enoxaparin Sodium Injection 40 mg once a day be 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.

Indication	Dose
Outpatient treatment of acute DVT without pulmonary embolism	1 mg/kg SC every 12 hours*
Unstable angina and non-Q-wave MI	1 mg/kg SC 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 IV bolus plus 1 mg/kg SC dose followed by 1 mg/kg SC every 12 hours (with aspirin)
Acute STEMI in patients ≥75 years of age	0.75 mg/kg SC every 12 hours (no bolus) (with aspirin)

• See recommended durations for Enoxaparin SC injection 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)

DOSE AND ADMINISTRATION
100 mg/mL concentration (3.1, 3.2)
• 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
150 mg/mL concentration (3.2)
• Graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL

CONTRAINDICATIONS
• Active major bleeding (4)
• Thrombocytopenia with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium (4)
• Hypersensitivity to enoxaparin sodium (4)
• Hypersensitivity to heparin or pork products (4)

WARNINGS AND PRECAUTIONS
• Increased risk of hemorrhage: Use with caution in patients at risk (5.1)
• Patients with mechanical heart valves: 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 bleeding, uncontrolled diabetes mellitus, renal dysfunction, or hemorrhage (5.3)
• History of heparin-induced thrombocytopenia: Use with caution (5.4)
• Thrombocytopenia: Monitor thrombocytopenia closely (5.5)
• Interchangeability with other heparins: Do not exchange with heparin or other heparin derivatives (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%) including anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, and nausea. (6.1)

TO REPORT SUSPECTED ADVERSE REACTIONS, contact Amphastar Pharmaceuticals, Inc. at 1-800-423-4136 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
Discontinue agents which may enhance hemorrhage risk prior to initiation of Enoxaparin Sodium Injection or conduct close clinical and laboratory monitoring (5.9, 7).
DRUG INTERACTIONS
Discontinue agents which may enhance hemorrhage risk prior to initiation of Enoxaparin Sodium Injection 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)
• Hepatic Impairment: Use with caution (8.6)
• Hypersensitivity: Use with caution (8.7)
• Low-Weight Patients: Observe for signs of bleeding (8.9)
• Obese Patients: Not adequately studied. Observe for thromboembolism (8.10)

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*Sections or subsections omitted from the full prescribing information are not listed

Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Enoxaparin Sodium Injection is 40 mg once a day administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Enoxaparin Sodium Injection has been administered in the controlled clinical trial.
Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism: In outpatient treatment, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Enoxaparin Sodium Injection is 1 mg/kg every 12 hours administered SC. In inpatient (hospital) treatment, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism who are not candidates for outpatient treatment, the recommended dose of Enoxaparin Sodium Injection is 1 mg/kg every 12 hours administered SC or 1.5 mg/kg once a day administered SC at the same time every day. In both outpatient and inpatient treatment, the recommended dose of Enoxaparin Sodium Injection is 1 mg/kg administered SC every 12 hours in conjunction with oral aspirin therapy (100 to 325 mg daily). Treatment with Enoxaparin Sodium Injection 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 days of Enoxaparin Sodium Injection has been administered in clinical trials [see Warnings and Precautions (5.2) and Clinical Studies (14.5)].
Treatment of Acute ST-Segment Elevation Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Enoxaparin Sodium Injection is a single IV bolus of 30 mg plus 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours (maximum 100 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 (2.3)]. All patients should receive aspirin as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated.
When administered in conjunction with a thrombolytic (fibrin-specific or non-fibrin specific), Enoxaparin Sodium Injection should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. In the pivotal clinical study, the Enoxaparin Sodium Injection treatment duration was 8 days or until hospital discharge, whichever came first. The maximum duration of treatment is not known. If the last Enoxaparin Sodium Injection SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of Enoxaparin Sodium Injection should be administered [see Warnings and Precautions (5.2)].

2.2 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 such patients should be observed closely for bleeding and symptoms of bleeding.
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	Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30 mL/minute)
Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily

Indication	Dosage Regimen
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Treatment of acute ST-segment elevation myocardial infarction in patients <75 years of age, when administered in conjunction with aspirin	30 mg single IV bolus plus 1 mg/kg SC dose followed by 1 mg/kg administered SC once daily
Treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, when administered in conjunction with aspirin	1 mg/kg administered SC 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 IV bolus. Initiate dosing with 0.75 mg/kg SC 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 (8.9) 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 Advertisements and Precautions
Enoxaparin Sodium Injection 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.
Enoxaparin Sodium Injection must not be administered by intramuscular injection. Enoxaparin Sodium Injection is intended for use under the guidance of a physician.
For subcutaneous administration, patients may self-inject only if their physicians determine that intradermal, intramuscular, or intravenous administration is not appropriate. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.
Subcutaneous Injection Technique: Patients should be lying down and Enoxaparin Sodium Injection 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 iliac crest and right upper arm, alternating sites with each injection. The prefilled syringe 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.
Enoxaparin Sodium Injection prefilled syringes and graduated prefilled syringes are for single, one-time use only and are available with a system that shields the needle after injection. Remove the prefilled syringe from the blister packaging by peeling the lid completely off the arrow as directed on the blister. Then gently lift the syringe straight up by grasping either the middle of the syringe or the needle guard. Do not remove by pulling on the plunger as this may damage the syringe.

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

5.9 Laboratory Tests
Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with enoxaparin sodium injection. 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 enoxaparin sodium injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of enoxaparin sodium injection in patients with significant renal impairment. If during enoxaparin sodium injection abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of enoxaparin sodium injection [see Clinical Pharmacology (12.3)].

6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
The following serious adverse reactions are also discussed in other sections of the labeling:
• Spinal/epidural hematoma [see Boxed Warning and Warnings and Precautions (5.1)]
• Increased Risk of Hemorrhage [see Warnings and Precautions (5.1)]
• Thrombocytopenia [see Warnings and Precautions (5.5)]
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. During clinical development for the approved indications, 15,918 patients were exposed to enoxaparin sodium. These included 1,228 for prophylaxis of deep vein thrombosis following abdominal surgery in patients at risk for thromboembolic complications, 1,368 for prophylaxis of deep vein thrombosis following hip or knee replacement surgery, 711 for prophylaxis of deep vein thrombosis in medical patients with severely restricted mobility during acute illness, 1,578 for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, 10,176 for treatment of acute ST-segment elevation myocardial infarction, and 857 for treatment of deep vein thrombosis with or without pulmonary embolism. Enoxaparin sodium doses in the clinical trials for prophylaxis of deep vein thrombosis following abdominal or hip or knee replacement surgery or in patients with severely restricted mobility during acute illness ranged from 40 mg SC once daily to 30 mg SC twice daily. In the clinical studies for prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction doses were 1 mg/kg every 12 hours and in the clinical studies for treatment of acute ST-segment elevation myocardial infarction enoxaparin sodium doses were a 30 mg IV bolus followed by 1 mg/kg every 12 hours SC.

Hemorrhage
The incidence of major hemorrhagic complications during enoxaparin sodium injection treatment has been low.
The following rates of major bleeding events have been reported during clinical trials with enoxaparin sodium injection [see Tables 2 to 7].

Table 2	Major Bleeding Episodes Following Abdominal and Colorectal Surgery ^a	
Indications	Enoxaparin Sodium Inj. ^b 40 mg q.d. SC	Heparin 5000 U q8h SC
Abdominal Surgery	n=555 23 (4%)	n=560 63 (11%)
Colorectal Surgery	n=673 28 (4%)	n=674 21 (3%)

3. DOSAGE FORMS AND STRENGTHS
Enoxaparin Sodium Injection is available in two concentrations:
3.1 100 mg/mL Concentration
• 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
3.2 150 mg/mL Concentration
• Graduated Prefilled Syringes 120 mg/0.8 mL, 150 mg/1 mL

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

5. WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
Cases of epidural or spinal hemorrhage and subsequent hematomas have been reported with the use of Enoxaparin Sodium Injection and epidural or spinal anesthesia/analgesia or spinal puncture procedures, resulting in long-term or permanent paralysis. The risk of these events is heightened with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting hemostasis such as NSAIDs, with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity [see Boxed Warning, Adverse Reactions (6.2) and Drug Interactions (7)]. To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin [see Clinical Pharmacology (12.3)]. Placement of epidural or spinal anesthesia/analgesia or spinal puncture is best performed when the anticoagulant effect of enoxaparin is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
Epidural or spinal anesthesia/analgesia or spinal puncture for at least 12 hours after administration of lower doses (30 mg once or twice daily or 40 mg once daily) of Enoxaparin Sodium Injection, and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of Enoxaparin Sodium Injection, should be avoided. If levels are still detectable at these time points, and these delays are not a guarantee that neuraxial hematoma will be avoided, Patients receiving the 0.75 mg/kg twice daily dose or the 1 mg/kg twice daily dose should not receive the second enoxaparin dose in the twice daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent Enoxaparin Sodium Injection dose after catheter removal cannot be made, considering delaying this next dose for at least 4 hours, based on a benefit-risk assessment considering both the anticoagulant effect of enoxaparin and the time points and delays are not a guarantee that neuraxial hematoma will be avoided. Patients receiving the 0.75 mg/kg twice daily dose or the 1 mg/kg twice daily dose should not receive the second enoxaparin dose in the twice daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent Enoxaparin Sodium Injection dose after catheter removal cannot be made, considering delaying this next dose for at least 4 hours, based on a benefit-risk assessment considering both the anticoagulant effect of enoxaparin and the time points and delays are not a guarantee that neuraxial hematoma will be avoided. 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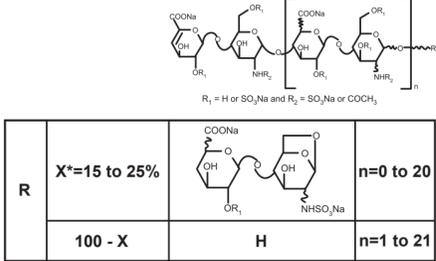
8.10 Obese Patients
Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses of Enoxaparin Sodium Injection in obese patients (BMI >30 kg/m²) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

10 OVERDOSEAGE
Accidental overdose following administration of enoxaparin sodium injection may lead to hemorrhagic complications. Intentional enoxaparin sodium injection may be largely neutralized by the slow IV injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of enoxaparin sodium injection injected. 1 mg protamine sulfate should be administered to neutralize 1 mg enoxaparin sodium injection, 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 enoxaparin sodium injection 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 completely neutralized (maximum about 60%). Particular care should be taken to avoid overdose with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, including anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

11 DESCRIPTION
Enoxaparin Sodium Injection is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin. The pH of the injection is 5.5 to 7.5.
11.2 Pharmacodynamics
Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzoyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enopyranosonic 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 to 8000 daltons ≥60%
2000 to 4000 daltons ≥28%
>8000 daltons ≤18%

STRUCTURAL FORMULA



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

Enoxaparin Sodium Injection 100 mg/mL Concentration contains 100 mg enoxaparin sodium (approximately anti-Factor Xa activity 1000 IU [with reference to the WHO. Second International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.
Enoxaparin Sodium Injection 150 mg/mL Concentration contains 150 mg enoxaparin sodium (approximately anti-Factor Xa activity 1500 IU [with reference to the WHO. Second International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The Enoxaparin Sodium Injection prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection. [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 (SC) 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 Xa activity versus time curves) compared to the ratios observed for heparin (mean±SD, 12.4±1.3), increases 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 SC 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 IV bolus immediately followed by a 1 mg/kg SC administration resulted in aPTT post-injection 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 SC 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 SC 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 SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg injection based on anti-Factor Xa activity is approximately 100% in healthy subjects.
A 30 mg IV bolus immediately followed by a 1 mg/kg SC 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 appear 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 was 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 was reached from day 1 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 SC injection of enoxaparin sodium was given to 25 healthy male and female subjects using a 100 mg/mL and 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 SC Once Daily Doses of Enoxaparin Sodium Using 100 mg/mL or 200 mg/mL Concentrations

Concentration	Anti-Xa	Anti-IIa	Hepstat	aPTT
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)
	200 mg/mL	3.5 (2-6)	4.5 (2.5-6)	3 (2-5)

* 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 (IV) dosing, the total body clearance of enoxaparin is 26 mL/min. After IV dosing of enoxaparin labeled with the gamma-emitter, ¹²⁵I, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine. 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 SC once a day dose.
Following SC 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 epimerization 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 A₀ derived from anti-Factor Xa values following single SC 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 A₀ derived from anti-Factor Xa values following single and multiple SC dosing in geriatric subjects were close to those observed in young subjects. Following once a day SC 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 Enoxaparin 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 30-50 mL/min) and moderately (creatinine clearance 10-30 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 85% 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 rates 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/m²) compared to non-obese control subjects, while A₀ 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 SC doses up to 20 mg/kg/day or 141 mg/mL/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 76 mg/mL/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m²).

13.2 Animal Toxicology and/or Pharmacology
A single SC 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 SC doses of enoxaparin up to 30 mg/kg/day corresponding to 211 mg/mL/day and 410 mg/mL/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
This study was conducted in 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. Enoxaparin sodium injection 40 mg SC, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was compared to heparin 5000 U every 8 hours SC in reducing the risk of DVT. The efficacy data are provided below [see Table 14].

Table 14
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	Dosing Regimen	
	Enoxaparin Sodium Inj. 40 mg q.d. SC n (%)	Heparin 5000 U q8h SC n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures	6 (1.1)	63 (11.3)
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)

¹ VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
² CI = Confidence Interval

In a second double-blind, parallel group study, enoxaparin sodium injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC 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 59.1 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 Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Colorectal Surgery

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

¹ VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
² CI = Confidence Interval

14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
Enoxaparin sodium injection has been shown to reduce the risk of post-operative deep vein thrombosis (DVT) following hip or knee replacement surgery.
In a double-blind study, enoxaparin sodium injection 30 mg every 12 hours SC 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 Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

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

¹ p value versus placebo = 0.0002
² p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of enoxaparin sodium injection 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, 3% 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 Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

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

¹ p value versus enoxaparin sodium injection 10 mg once a day = 0.0008
² p value versus enoxaparin sodium injection 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 regimen in a double-blind study. Enoxaparin sodium injection 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 distal DVT after surgery was significantly lower for enoxaparin sodium injection compared to placebo. The efficacy data are provided below [see Table 18].

Table 18
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery

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

¹ p value versus placebo = 0.0001
² CI = Confidence Interval
³ CI = Confidence Interval
CL = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium injection 30 mg every 12 hours SC in patients undergoing elective knee replacement surgery was compared to heparin 5000 U every 8 hours SC. 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, 3.3% Black, and 0.6% others. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for enoxaparin sodium injection 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 enoxaparin sodium injection 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 enoxaparin sodium injection 40 mg (n=90) once a day SC or 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 enoxaparin sodium injection compared to placebo. The efficacy data are provided below [see Table 19].

Table 19
Efficacy of Enoxaparin Sodium Injection in the Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

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

¹ p value versus placebo = 0.008
² CI = Confidence Interval
p value versus placebo = 0.537

In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin sodium injection 40 mg SC, 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 enoxaparin sodium injection 40 mg (n=131) once a day SC or 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 enoxaparin sodium injection compared to placebo, with a statistically significant difference in both total DVT (enoxaparin sodium injection 21 [16%] versus placebo 45 [34%]; p=0.001) and proximal DVT (enoxaparin sodium injection 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, enoxaparin sodium injection 20 mg or 40 mg once a day SC 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 receiving ventilatory support); acute infection (excluding septic shock); or acute thrombotic 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 18 to 92 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, enoxaparin sodium injection significantly reduced the incidence of DVT as compared to placebo. The efficacy data are provided below [see Table 20].

Table 20
Efficacy of Enoxaparin Sodium Injection in the Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	Dosing Regimen		
	Enoxaparin Sodium Inj. 20 mg q.d. SC n (%)	Enoxaparin Sodium Inj. 40 mg q.d. SC n (%)	Placebo n (%)
All Treated Medical Patients During Acute Illness	351 (100)	360 (100)	362 (100)
Treatment Failures ¹	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)

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 enoxaparin sodium injection 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) enoxaparin sodium injection 1.5 mg/kg once a day SC, (ii) enoxaparin sodium injection 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 according to PT) to achieve an International Normalization Ratio (INR) of 2.0 to 3.0, commencing within 72 hours of initiation of enoxaparin sodium injection or standard heparin therapy, and continuing for 90 days. Enoxaparin sodium injection or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both enoxaparin sodium injection 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 Enoxaparin Sodium Injection in Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

Indication	Dosing Regimen ¹		
	Enoxaparin Sodium Inj. 1.5 mg/kg q.d. SC n (%)	Enoxaparin Sodium Inj. 1 mg/kg q12h SC n (%)	Heparin aPTT Adjusted IV Therapy n (%)
	All Treated DVT Patients with or without PE	298 (100)	312 (100)
Treatment Failures	13 (4.4)	9 (2.9)	12 (4.1)
Total DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
Proximal DVT (%)	17 (11)	8 (4 ²)	9 (5)

¹ All patients were also treated with warfarin sodium commencing within 72 hours of enoxaparin sodium injection or standard heparin therapy.
² VTE = venous thromboembolic event (DVT and/or PE).

The 95% Confidence Intervals for the treatment differences for total VTE were: enoxaparin sodium injection 1 mg/kg every 12 hours SC or heparin IV bolus (5000 IU) enoxaparin sodium injection 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 enoxaparin sodium injection 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 outpatient because of geographic inaccessibility. Eligible patients were randomized to either enoxaparin sodium injection 1 mg/kg every 12 hours SC or heparin IV 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. Enoxaparin sodium injection or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both enoxaparin sodium injection regimens were 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 Enoxaparin Sodium Injection in Treatment of Deep Vein Thrombosis

Indication	Dosing Regimen ¹	
	Enoxaparin Sodium Inj. 1 mg/kg q12h SC n (%)	Heparin aPTT Adjusted IV Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome		
Total VTE (%)	13 (5.3 ²)	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)

¹ All patients were also treated with warfarin sodium commencing on the evening of the second day of enoxaparin sodium injection or standard heparin therapy.
² VTE = venous thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]).

³ p value versus placebo = 0.013
⁴ CI = Confidence Interval

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 enoxaparin sodium injection 1 mg/kg every 12 hours SC or heparin IV bolus (5000 IU) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled