

HIGHLIGHTS OF PRESCRIBING INFORMATION

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 HEMATOMAS	
See full prescribing information for complete boxed warning.	
Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:	
• Use of indwelling epidural catheters	
• Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and 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. (5.1, 7)	

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 (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)

DOSE AND ADMINISTRATION

See full prescribing information for dosing and administration information. (2)

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DOSE FORMS AND STRENGTHS

- 100 mg per mL concentration (3):
- Single-Dose Prefilled Syringes: 30 mg per 0.3 mL, 40 mg per 0.4 mL
 - Single-Dose Graduated Prefilled Syringes: 60 mg per 0.6 mL, 80 mg per 0.8 mL, 100 mg per mL
- 150 mg per mL concentration (3):
- Single-Dose Graduated Prefilled Syringes: 120 mg per 0.8 mL, 150 mg per mL

CONTRAINDICATIONS

- Active major bleeding (4)
 - History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (4)
 - Hypersensitivity to enoxaparin sodium (4)
 - Hypersensitivity to heparin or pork products (4)
- WARNINGS AND PRECAUTIONS**
- Increased Risk of Hemorrhage: Monitor for signs of bleeding. (5.1, 5.2, 5.3)
 - Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis. (5.4)
 - Thrombocytopenia: Monitor platelet count closely. (5.5)
 - Interchangeability with other heparins: Do not exchange with heparin or other LMWHs. (5.6)
 - Increased Risk of Thrombosis in Pregnant Women with Mechanical Prosthetic Heart Valves: Women and their fetuses may be at increased risk. Monitor more frequently and adjust dosage as needed. (5.7)

ADVERSE REACTIONS

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

To report suspected ADVERSE REACTIONS, contact Meitheal Pharmaceuticals Inc. at 1-844-824-8426 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Discontinue agents which may enhance hemorrhage risk prior to initiation of enoxaparin sodium or conduct close clinical and laboratory monitoring. (2.6, 7)

USE IN SPECIFIC POPULATIONS

- Severe Renal Impairment: Adjust dose for patients with creatinine clearance <30 mL/min. (2.3, 8.7)
- Geriatric Patients: Monitor for increased risk of bleeding. (8.5)
- Low-Weight Patients: Observe for signs of bleeding. (8.8)

SEE 17 FOR PATIENT COUNSELING INFORMATION.

Revised: 07/2019

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

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, and 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)*].

- INDICATIONS AND USAGE
 - Prophylaxis of Deep Vein Thrombosis
- 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
 - in patients undergoing knee replacement surgery
 - in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness
- 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
- 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 DOSE AND ADMINISTRATION

2.1 Pretreatment Evaluation

Evaluate all patients for a bleeding disorder before starting enoxaparin sodium injection treatment, unless treatment is urgently needed.

2.2 Adult Dosage

Abdominal Surgery

The recommended dose of enoxaparin sodium injection is **40 mg** administered subcutaneous injection once a day (with the initial dose given 2 hours prior to surgery) in patients undergoing abdominal surgery who are at risk for thromboembolic complications. The usual duration of administration is 7 to 10 days [see *Clinical Studies (14.1)*].

Hip or Knee Replacement Surgery

The recommended dose of enoxaparin sodium injection is **30 mg every 12 hours** administered by subcutaneous injection in patients undergoing hip or knee replacement surgery. Administer the initial dose 12 to 24 hours after surgery, provided that hemostasis has been established. The usual duration of administration is 7 to 10 days [see *Clinical Studies (14.2)*].

A dose of enoxaparin sodium injection of **40 mg once a day** subcutaneously may be considered for hip replacement surgery for up to 3 weeks. Administer the initial dose 12 (±3) hours prior to surgery.

Medical Patients During Acute Illness

The recommended dose of enoxaparin sodium injection is **40 mg once a day** administered by subcutaneous injection for medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness. The usual duration of administration is 6 to 11 days [see *Clinical Studies (14.3)*].

Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

The recommended dose of enoxaparin sodium injection is **1 mg/kg every 12 hours** administered subcutaneously in patients with acute deep vein thrombosis without pulmonary embolism, who can be treated at home in an outpatient setting.

The recommended dose of enoxaparin sodium injection is **1 mg/kg every 12 hours** administered subcutaneously or **1.5 mg/kg once a day** administered subcutaneously at the same time every day for **inpatient (hospital) treatment** of 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).

In both outpatient and inpatient (hospital) treatments, initiate warfarin sodium therapy when appropriate (usually within 72 hours of enoxaparin sodium injection). Continue enoxaparin sodium injection for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio ≥2.3). The average duration of administration is 7 days [see *Clinical Studies (14.4)*].

Unstable Angina and Non-Q-Wave Myocardial Infarction

The recommended dose of enoxaparin sodium injection is **1 mg/kg** administered subcutaneously every 12 hours in conjunction with oral aspirin therapy (100 to 325 mg once daily) in patients with unstable angina or non-Q-wave myocardial infarction. Treat with enoxaparin sodium injection for a minimum of 2 days and continue until clinical stabilization. The usual duration of treatment is 2 to 8 days [see *Warnings and Precautions (5.2) and Clinical Studies (14.5)*].

Treatment of Acute ST-Segment Elevation Myocardial Infarction

The recommended dose of enoxaparin sodium injection is a **single intravenous bolus of 30 mg** plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg administered subcutaneously every 12 hours (maximum 100 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining doses) in patients with acute ST-segment elevation myocardial infarction. Reduce the dosage in patients ≥75 years of age [see *Dosage and Administration (2.4)*]. Unless contraindicated, administer aspirin to all patients as soon as they are identified as having STEMI and continue dosing with 75 to 325 mg once daily.

When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), administer enoxaparin sodium injection between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. The usual duration of enoxaparin sodium injection therapy is 8 days or until hospital discharge.

For patients managed with percutaneous coronary intervention (PCI), if the last enoxaparin sodium injection subcutaneous administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last enoxaparin sodium injection subcutaneous administration was given more than 8 hours before balloon inflation, administer an intravenous bolus of 0.3 mg/kg of enoxaparin sodium injection [see *Warnings and Precautions (5.2)*].

2.3 Dose Reduction for Patients with Severe Renal Impairment

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

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered subcutaneously once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered subcutaneously once daily
Prophylaxis in medical patients during acute illness	30 mg administered subcutaneously once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered subcutaneously once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered subcutaneously once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered subcutaneously once daily
Treatment of patients ST-segment elevation myocardial infarction in patients <75 years of age, when administered in conjunction with aspirin	30 mg single intravenous bolus plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg administered subcutaneously once daily

Treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, when administered in conjunction with aspirin	1 mg/kg administered subcutaneously once daily (no initial bolus)
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Although no dose adjustment is recommended in patients with creatinine clearance 30 to 50 mL/min and creatinine clearance 50 to 80 mL/min, observe these patients frequently for signs and symptoms of bleeding.

2.4 Recommended Dosage for Geriatric Patients with Acute ST-Segment Elevation Myocardial Infarction

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

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

2.5 Administration

Do not administer enoxaparin sodium injection by intramuscular injection.

Administer enoxaparin sodium injection by intravenous or subcutaneous injection only.

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.

Patients may self-inject by the subcutaneous route of administration only after their physicians determine that it is appropriate and with medical follow-up, as necessary. Provide proper training in subcutaneous injection technique before allowing self-injection (with or without the assistance of an injection device).

Subcutaneous Injection Technique

- Position patients in a supine position for enoxaparin sodium injection administration by deep subcutaneous injection.
- Do not expel the air bubble from the prefilled syringes before the injection, to avoid the loss of drug.
- Alternate injection sites between the left and right anterolateral and left and right posterolateral abdominal wall.
- Introduce the whole length of the needle into a skin fold held between the thumb and forefinger; hold the skin fold 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 at the arrow as directed on the blister. Do not remove by pulling on the plunger as this may damage the syringe.

- Remove the needle shield by pulling it straight off the syringe (see Figure A). If less than the full syringe volume is needed to administer the prescribed dose, eject syringe contents until the prescribed dose is left in the syringe.

Figure A



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

Figure B



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

Figure C



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

Figure D



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

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

Use the multiple-dose vial for intravenous injections. Administer enoxaparin sodium injection through an intravenous line. Do not mix or coadminister enoxaparin sodium injection with other medications. Flush the intravenous access device with a sufficient volume of saline or dextrose solution prior to and following the intravenous bolus administration of enoxaparin sodium injection, to prevent mixing of drugs. Enoxaparin sodium injection is compatible with normal saline solution (0.9%) or 5% dextrose in water.

2.6 Monitoring for Safety

During surgery monitor complete blood counts including platelets and stool occult blood.

Assess for signs and symptoms of bleeding.

In patients with renal impairment anti-Factor Xa levels may be used to monitor the anticoagulant effects of enoxaparin sodium injection.

If during enoxaparin sodium injection therapy 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)*].

- DOSE FORMS AND STRENGTHS
- Enoxaparin Sodium Injection, USP is available in two concentrations:
- 100 mg per mL Concentration**
- Single-Dose Prefilled Syringes 30 mg per 0.3 mL, 40 mg per 0.4 mL
 - Single-Dose Graduated Prefilled Syringes 60 mg per 0.6 mL, 80 mg per 0.8 mL, 100 mg per mL
- 150 mg per mL Concentration**
- Single-Dose Graduated Prefilled Syringes 120 mg per 0.8 mL, 150 mg per mL
- CONTRAINDICATIONS
- Enoxaparin sodium is contraindicated in patients with:
- Active major bleeding
 - History of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies [see *Warnings and Precautions (5.4)*]

Enoxaparin sodium is contraindicated in patients with:

- Active major bleeding
- History of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies [see *Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of 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 higher with the use of postoperative indwelling epidural catheters, with the concurrent use of additional drugs affecting hemostasis such as NSAIDs, 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 or removal of an epidural catheter or lumbar 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.

Placement or removal of a catheter should be delayed 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. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuronal hematomas 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 dose after catheter removal cannot be made, consider delaying this next dose for at least four hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance <30 mL/minute, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin sodium (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day) [see *Clinical Pharmacology (12.3)*].

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), and bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematomas are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

Use enoxaparin sodium injection 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 before 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 enoxaparin sodium injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

5.2 Increased Risk of Bleeding following 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 enoxaparin sodium injection 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 intravenous/subcutaneous enoxaparin sodium injection. 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 Increased Risk of Bleeding in Patients with Concomitant Medical Conditions

Enoxaparin sodium should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage.

5.4 Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis

Enoxaparin sodium may cause Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia with Thrombosis (HITTS). HITTS may lead to organ infarction, limb ischemia, or death. Monitor thrombocytopenia of any degree closely.

Use of enoxaparin sodium in patients with a history of immune-mediated HIT within the past 100 days or in the presence of circulating antibodies is contraindicated [see *Contraindications (4)*].

Circulating antibodies may persist for several years.

Only use enoxaparin sodium in patients with a history of HIT if more than 100 days have elapsed since the prior HIT episode and no circulating antibodies are present. Because HIT may still occur in these circumstances, the decision to use enoxaparin sodium in such a case must be made only after a careful benefit-risk assessment and after non-heparin alternative treatments are considered.

5.5 Thrombocytopenia

Thrombocytopenia can occur with the administration of enoxaparin sodium.

Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given enoxaparin sodium, 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 enoxaparin sodium, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, enoxaparin sodium should be discontinued.

5.6 Interchangeability with other Heparins

Enoxaparin sodium 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-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

5.7 Increased Risk of Thrombosis in Pregnant Women with Mechanical Prosthetic Heart Valves

Use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves may result in valve thrombosis. 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. No patients in the heparin/warfarin group (0 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-Factor Xa levels, and adjustment of dosage may be needed [see *Use in Specific Populations (8.6)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are also discussed in other sections of the labeling:

- Spinal/epidural hematomas [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Increased Risk of Hemorrhage [see *Warnings and Precautions (5.1*

8.2 Lactation

Risk Summary

It is unknown whether enoxaparin sodium is excreted in human milk. In lactating rats, the passage of enoxaparin or its metabolites in the milk is very limited. There is no information available on the effect of enoxaparin or its metabolites on the breastfed child, or on the milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for enoxaparin sodium and any potential adverse effects on the breastfed child from enoxaparin sodium or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of enoxaparin sodium in pediatric patients have not been established. Enoxaparin sodium is not approved for use in neonates or infants.

8.5 Geriatric Use

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

Over 2800 patients, 65 years and older, have received enoxaparin sodium in clinical trials. The efficacy of enoxaparin sodium in the geriatric (>65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of enoxaparin sodium were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when enoxaparin sodium was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of enoxaparin sodium-associated bleeding increased with age. Serious adverse events increased with age for patients receiving enoxaparin sodium. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin sodium between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Enoxaparin sodium 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 reported to decreased renal function should be considered [see *Warnings and Precautions* (2.6) and *Clinical Pharmacology* (12.3)].

Treatment of Acute ST-Segment Elevation Myocardial Infarction

In the clinical study for treatment of acute ST-segment elevation myocardial infarction, there was no evidence of difference in efficacy between patients <75 years of age (n=1241) and patients less than 75 years of age (<9015). Patients <75 years of age did not receive a 30 mg intravenous bolus prior to the normal dosage regimen and had their subcutaneous dose adjusted to 0.75 mg/kg every 12 hours [see *Dosage and Administration* (2.4)]. The incidence of bleeding complications was higher in patients <65 years of age as compared to younger patients (<65 years).

8.6 Patients with Mechanical Prosthetic Heart Valves

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

8.7 Renal Impairment

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with creatinine clearance 30 to <50 mL/min and creatinine clearance 50 to 80 mL/min [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3)]. In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia [see *Adverse Reactions* (6.2)].

8.8 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). Observe low-weight patients frequently for signs and symptoms of bleeding [see *Clinical Pharmacology* (12.3)].

8.9 Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses of enoxaparin sodium in obese patients (BMI >30 kg/m²) has not been fully determined and there is no consensus for dose adjustment. Observe these patients carefully for signs and symptoms of thromboembolism.

10 OVERDOSAGE

Accidental overdose following administration of enoxaparin sodium may lead to hemorrhagic complications. Injected enoxaparin sodium may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of enoxaparin sodium injected: 1 mg protamine sulfate should be administered to neutralize 1 mg enoxaparin sodium. 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 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 overdose with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

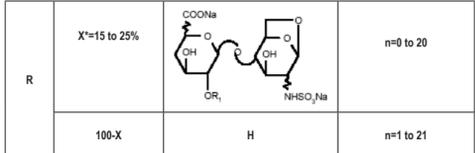
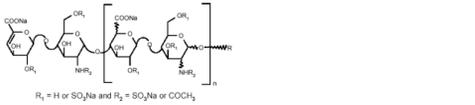
11 DESCRIPTION

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

Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-eneopyranosonic acid group (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 a 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 4,500 daltons. The molecular weight distribution is:



STRUCTURAL FORMULA



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

Enoxaparin Sodium Injection, USP 100 mg per mL. Concentration contains 10 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1,000 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

Enoxaparin Sodium Injection, USP 150 mg per mL. Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1,500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The Enoxaparin Sodium Injection, USP 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/Storage and Handling* (16)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean ±SD, 14.0±3.1) based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean ±SD, 1.22±0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose (100 mg/mL concentration), administered subcutaneously every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n=1607). A 30 mg intravenous bolus immediately followed by a 1 mg/kg subcutaneous administration resulted in aPTT postinjection values of 50 seconds. The average aPTT prolongation value on Day 1 was about 15% higher than on Day 4.

12.3 Pharmacokinetics

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens. In a double-blind study, enoxaparin sodium 30 mg every 12 hours subcutaneously was compared to placebo in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the study and 131 patients were treated, of which 99 had total knee replacement and 32 had either unicompartmental knee replacement or total 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 enoxaparin sodium compared to placebo. The efficacy data are provided below (see Table 18).

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)
Treatment Failures		
Total DVT* (%)	5 (10) [†]	23 (46)
Proximal DVT (%)	1 (2) [‡]	11 (22)

* p value versus placebo = 0.0002
† p value versus placebo = 0.0134

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)
Treatment Failures		
Total DVT* (%)	40 (25)	22 (11) [†]
Proximal DVT (%)	17 (11)	8 (4) [‡]
		9 (5)

* p value versus placebo = 0.0008
† p value versus placebo = 0.0168

Table 20: Efficacy of Enoxaparin Sodium in the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures		
Total DVT* (%)	5 (11) [†]	32 (62)
Proximal DVT (%)	0 (0) [‡]	7 (13)
		5 (6) [§]
		7 (13)

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

Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium 30 mg every 12 hours subcutaneously in patients undergoing elective knee replacement surgery was compared to heparin 5,000 U every 8 hours subcutaneously. A total of 453 patients were randomized in the study and all were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.8% 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 18).

Table 13: Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg Subcutaneous Once-Daily Doses of Enoxaparin Sodium Using 100 mg/mL or 200 mg/mL Concentrations

Concentration	Anti-IIa				Hepstat				aPTT						
	Concentration	Anti-IIa	Anti-IIa	Hepstat	aPTT	Concentration	Anti-IIa	Anti-IIa	Hepstat	aPTT	Concentration	Anti-IIa	Anti-IIa	Hepstat	aPTT
A ₀₋₆ (U/mL or Δ sec)	100 mg/mL	1.37 (±0.23)	0.23 (±0.05)	105 (±17)	19 (±5)	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	111 (±17)	22 (±7)	90% CI	102% to 110%	4.2 (2 to 6)	2.5 (2 to 4.5)	3 (2 to 4.5)
	200 mg/mL	3.5 (2 to 6)	4 (2 to 5)	2.5 (2 to 4.5)	3 (2 to 4.5)	90% CI	102% to 110%	4.2 (2 to 6)	2.5 (2 to 4.5)	3 (2 to 4.5)					
t _{1/2α} (h)	100 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)		200 mg/mL	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)		90% CI	105% to 112%	103% to 109%		
	200 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)		90% CI	105% to 112%	103% to 109%							

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

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

Elimination
Following intravenous dosing, the total body clearance of enoxaparin is 26 mL/min. After intravenous dosing of enoxaparin labeled with the ¹⁴C isotope, 48 to 20% of the administered dose of enoxaparin sodium activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after a single subcutaneous dose to about 7 hours after repeated dosing. Significant anti-Factor Xa activity persists in plasma for about 12 hours following a 40 mg subcutaneous once a day dose.

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

Metabolism
Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments is about 4% of the dose.

Special Populations
Gender
Apparent clearance and A₀₋₆ derived from anti-Factor Xa values following single and multiple subcutaneous dosing in geriatric subjects were close to those observed in young subjects.

Following once a day subcutaneous dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value [see

2.1 Dosage and Administration (2.1) and Use in Specific Populations (8.1)

Renal Impairment

A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady state, is marginally increased in patients with creatinine clearance 50 to 80 mL/min and patients with creatinine clearance 30 to <50 mL/min renal impairment after repeated subcutaneous 40 mg once-daily doses. In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC at steady state is significantly increased on average by 65% after repeated subcutaneous 40 mg once-daily doses [see *Dosage and Administration* (2.3) and *Use in Specific Populations* (8.7)].

Hemodialysis

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

Hepatic Impairment

Studies with enoxaparin in patients with hepatic impairment have not been conducted and the impact of hepatic impairment on the exposure to enoxaparin is unknown.

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 to 48 kg/m²) compared to non-obese control subjects, while A₀₋₆ 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* (8.8)].

Pharmacokinetic Interaction

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2 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).

13.2 Animal Toxicology and/or Pharmacology

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

13.3 Reproductive and Developmental Toxicology

Toxicology studies have been conducted in pregnant rats and rabbits at subcutaneous doses of enoxaparin up to 30 mg/kg/day corresponding to 211 mg/m²/day and 410 mg/m²/day in rats and rabbits respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin.

14 CLINICAL STUDIES

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

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

In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Asian and 0.4% others. Enoxaparin sodium 40 mg subcutaneously, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5,000 U every 8 hours subcutaneously in reducing the risk of DVT. The efficacy data are provided below (see Table 14).

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Heparin 5,000 U q8h subcutaneously n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures		
Total VTE* (%)	56 (10.1)	63 (11.3)
	(95% CI: 8 to 13)	(95% CI: 9 to 14)
DVT Only (%)	54 (9.7)	61 (10.9)
	(95% CI: 7 to 12)	(95% CI: 8 to 13)

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

In a second double-blind, parallel group study, enoxaparin sodium 40 mg subcutaneously once a day was compared to heparin 5,000 U every 8 hours subcutaneously in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below (see Table 15).

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Heparin 5,000 U q8h subcutaneously n (%)
All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures		
Total VTE* (%)	48 (7.1)	45 (6.7)
	(95% CI: 5 to 9)	(95% CI: 5 to 9)
DVT Only (%)	47 (7.0)	44 (6.5)
	(95% CI: 5 to 9)	(95% CI: 5 to 8)

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

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

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

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)
Treatment Failures		
Total DVT* (%)	5 (10) [†]	23 (46)
Proximal DVT (%)	1 (2) [‡]	11 (22)

* p value versus placebo = 0.0002
† p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of enoxaparin sodium 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 89 years (mean age 64.7 years) with 53% men and 37% women. Patients were 93% Caucasian, 6% Black, <1% Asian, and 1% others. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The efficacy data are provided below (see Table 17).

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)
Treatment Failures		
Total DVT* (%)	40 (25)	22 (11) [†]
Proximal DVT (%)	17 (11)	8 (4) [‡]
		9 (5)

* p value versus placebo = 0.0008
† p value versus placebo = 0.0168

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures		
Total DVT* (%)	5 (11) [†]	32 (62)
Proximal DVT (%)	0 (0) [‡]	7 (13)
		5 (6) [§]
		7 (13)

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

Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium 30 mg every 12 hours subcutaneously in patients undergoing elective knee replacement surgery was compared to heparin 5,000 U every 8 hours subcutaneously. A total of 453 patients were randomized in the study and all were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.8% 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 18).

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

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)
Treatment Failures		
Total DVT* (%)	40 (25)	22 (11) [†]
Proximal DVT (%)	17 (11)	8 (4) [‡]
		9 (5)

* p value versus placebo = 0.0008
† p value versus placebo = 0.0168

Table 20: Efficacy of Enoxaparin Sodium in the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery

Indication	Dosing Regimen	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures		
Total DVT* (%)	5 (11) [†]	32 (62)
Proximal DVT (%)	0 (0) [‡]	7 (13)
		5 (6) [§]
		7 (13)

* p value versus placebo = 0.0001
† CI = Confidence Interval
‡ p value versus placebo =

HIGHLIGHTS OF PRESCRIBING INFORMATION

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 HEMATOMAS

See full prescribing information for complete boxed warning.

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

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and 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. (5.1, 7)

INDICATIONS AND USAGE

- Enoxaparin Sodium Injection is a low molecular weight heparin (LMWH) indicated for:
- Prophylaxis of deep vein thrombosis (DVT) in 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)

DOSE AND ADMINISTRATION

See full prescribing information for dosing and administration information. (2)

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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, and 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

1.1 Prophylaxis of Deep Vein Thrombosis

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
- in patients undergoing 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

2.1 Pretreatment Evaluation

Evaluate all patients for a bleeding disorder before starting enoxaparin sodium injection treatment, unless treatment is urgently needed.

2.2 Adult Dosage

Abdominal Surgery

The recommended dose of enoxaparin sodium injection is 40 mg by subcutaneous injection once a day (with the initial dose given 2 hours prior to surgery) in patients undergoing abdominal surgery who are at risk for thromboembolic complications. The usual duration of administration is 7 to 10 days [see Clinical Studies (14.1)].

Hip or Knee Replacement Surgery

The recommended dose of enoxaparin sodium injection is 30 mg every 12 hours administered by subcutaneous injection in patients undergoing hip or knee replacement surgery. Administer the initial dose 12 to 24 hours after surgery, provided that hemostasis has been established. The usual duration of administration is 7 to 10 days [see Clinical Studies (14.2)].

A dose of enoxaparin sodium injection of 40 mg once a day subcutaneously may be considered for hip replacement surgery for up to 3 weeks. Administer the initial dose 12 (±3) hours prior to surgery.

Medical Patients during Acute Illness

The recommended dose of enoxaparin sodium injection is 40 mg once a day administered by subcutaneous injection for medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness. The usual duration of administration is 6 to 11 days [see Clinical Studies (14.3)].

Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

The recommended dose of enoxaparin sodium injection is 1 mg/kg every 12 hours administered subcutaneously in patients with acute deep vein thrombosis without pulmonary embolism, who can be treated at home in an outpatient setting.

The recommended dose of enoxaparin sodium injection is 1 mg/kg every 12 hours administered subcutaneously or 1.5 mg/kg once a day administered subcutaneously at the same time every day for inpatient (hospital) treatment of 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).

In both outpatient and inpatient (hospital) treatments, initiate warfarin sodium therapy when appropriate (usually within 72 hours of enoxaparin sodium injection). Continue enoxaparin sodium injection for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2 to 3). The average duration of administration is 7 days [see Clinical Studies (14.4)].

Unstable Angina and Non-Q-Wave Myocardial Infarction

The recommended dose of enoxaparin sodium injection is 1 mg/kg administered subcutaneously every 12 hours in conjunction with oral aspirin therapy (100 to 325 mg once daily) in patients with unstable angina or non-Q-wave myocardial infarction. Treat with enoxaparin sodium injection for a minimum of 2 days and continue until clinical stabilization. The usual duration of treatment is 2 to 8 days [see Warnings and Precautions (5.2) and Clinical Studies (14.5)].

Treatment of Acute ST-Segment Elevation Myocardial Infarction

The recommended dose of enoxaparin sodium injection is a single intravenous bolus of 30 mg plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg administered subcutaneously every 12 hours (maximum 100 mg) for the first two doses only, followed by 1 mg/kg dosing for the remaining doses) in patients with acute ST-segment elevation myocardial infarction. Reduce the dosage in patients ≥75 years of age [see Dosage and Administration (2.4)]. Unless contraindicated, administer aspirin to all patients as soon as they are identified as having STEMI and continue dosing with 75 to 325 mg once daily.

When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), administer enoxaparin sodium injection between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. The usual duration of enoxaparin sodium injection therapy is 8 days or until hospital discharge.

For patients managed with percutaneous coronary intervention (PCI), if the last enoxaparin sodium injection subcutaneous administration was given less than 8 hours before PCI, no additional dosing is needed. If the last enoxaparin sodium injection subcutaneous administration was given more than 8 hours before balloon inflation, administer an intravenous bolus of 0.3 mg/kg of enoxaparin sodium injection [see Warnings and Precautions (5.2)].

2.3 Dose Reduction for Patients with Severe Renal Impairment

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

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

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

Although no dose adjustment is recommended in patients with creatinine clearance 30 to 50 mL/min and creatinine clearance 50 to 80 mL/min, observe these patients frequently for signs and symptoms of bleeding.

DOSE FORMS AND STRENGTHS

- 100 mg per mL concentration (3):
- Single-dose prefilled syringes: 30 mg per 0.3 mL, 40 mg per 0.4 mL
 - Single-dose graduated prefilled syringes: 60 mg per 0.6 mL, 80 mg per 0.8 mL, 100 mg per mL
- 150 mg per mL concentration (3):
- Single-dose graduated prefilled syringes: 120 mg per 0.8 mL, 150 mg per mL

CONTRAINDICATIONS

- Active major bleeding (4)
- History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (4)
- Hypersensitivity to enoxaparin sodium (4)
- Hypersensitivity to heparin or pork products (4)

WARNINGS AND PRECAUTIONS

- Increased Risk of Hemorrhage: Monitor for signs of bleeding. (5.1, 5.2, 5.3)
- Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis. (5.4)
- Thrombocytopenia: Monitor platelet count closely. (5.5)
- Interchangeability with other heparins: Do not exchange with heparin or other LMWHs. (5.6)
- Increased Risk of Thrombosis in Pregnant Women with Mechanical Prosthetic Heart Valves: Women and their fetuses may be at increased risk. Monitor more frequently and adjust dosage as needed. (5.7)

ADVERSE REACTIONS

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

To report suspected ADVERSE REACTIONS, contact Medical Pharmacologists Inc. at 1-844-824-8426 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Discontinue agents which may enhance hemorrhagic risk prior to initiation of enoxaparin sodium or conduct close clinical and laboratory monitoring. (2.6, 7)

USE IN SPECIFIC POPULATIONS

- Severe Renal Impairment: Adjust dose for patients with creatinine clearance <30 mL/min. (2.3, 8.7)
- Geriatric Patients: Monitor for increased risk of bleeding. (8.5)
- Low-Weight Patients: Observe for signs of bleeding. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

WARNINGS AND PRECAUTIONS

5 Increased Risk of 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 higher with the use of postoperative indwelling epidural catheters, with the concomitant use of neuraxial anesthesia or spinal puncture, 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 (5.2) and Drug Interactions (7)].

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium injection and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium injection [see Clinical Pharmacology (12.3)]. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin sodium injection is low, however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Placement or removal of a catheter should be delayed 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. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial hematomas 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 sodium injection 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, consider delaying this next dose for at least 48 hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance <30 mL/min, additional considerations are necessary because elimination of enoxaparin sodium injection is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin sodium injection (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day) [see Clinical Pharmacology (12.3)].

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), and bowel and/or bladder dysfunction. Instruct patients to report immediately any experience any of the above signs or symptoms. If signs or symptoms of spinal cord compression are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

Use enoxaparin sodium injection with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerated 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 enoxaparin sodium injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

5.2 Increased Risk of Bleeding following 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 enoxaparin sodium injection 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 after the procedure. If a manual compression method is used, sheath should be removed 6 hours after the last intravenous/subcutaneous enoxaparin sodium injection. 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 Increased Risk of Bleeding in Patients with Concomitant Medical Conditions

Enoxaparin sodium should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage.

5.4 Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis

Enoxaparin sodium may cause heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis (HITTS). HITTS may lead to organ infarction, limb ischemia, or death. Monitor thrombocytopenia of any degree closely.

Use of enoxaparin sodium in patients with a history of immune-related HIT within the past 100 days or in the presence of circulating antibodies is contraindicated [see Contraindications (4)]. Circulating antibodies may persist for several years.

Only use enoxaparin sodium in patients with a history of HIT if more than 100 days have elapsed since the prior HIT episode and no circulating antibodies are present. Because HIT may still be present in these circumstances, the decision to use enoxaparin sodium in such a case must be made only after a careful benefit-risk assessment and after non-heparin alternative treatments are considered.

5.5 Thrombocytopenia

Thrombocytopenia can occur with the administration of enoxaparin sodium. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given enoxaparin sodium, 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 enoxaparin sodium, in 0.2% of patients given heparin and 0.4% of patients given placebo.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, enoxaparin sodium should be discontinued.

5.6 Interchangeability with other Heparins

Enoxaparin sodium 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-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

5.7 Increased Risk of Thrombosis in Pregnant Women with Mechanical Prosthetic Heart Valves

Use of enoxaparin sodium injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves may result in valve thrombosis. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin sodium injection (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. No patients in the heparin sodium group (0 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 sodium injection for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at a higher risk for thromboembolism during pregnancy and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion, and preterm delivery. Instruct patients to report immediately if they experience any of the above signs or symptoms, and adjusting of dosage may be needed [see Use in Specific Populations (8.6)].

6 ADVERSE REACTIONS

The following serious adverse reactions are also discussed in other sections of the labeling:

- Spinal/epidural hematomas [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)]

6.1 Clinical Trials Experience

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, 1,228 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-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 medical patients with severely restricted mobility during acute illness ranged from 40 mg subcutaneously once daily to 30 mg subcutaneously twice daily. In the clinical studies for prophylaxis of ischemic complications and non-Q-wave myocardial infarction, enoxaparin sodium 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 intravenous bolus followed by 1 mg/kg every 12 hours subcutaneously.

Hemorrhage

The following rates of major bleeding events have been reported during clinical trials with enoxaparin sodium (see Tables 2 to 7).

Table 2: Major Bleeding Episodes following Abdominal and Colorectal Surgery^a

Indications	Dosing Regimen		Heparin 15,000 U q12h subcutaneously
	Enoxaparin Sodium 40 mg daily subcutaneously	Enoxaparin Sodium 30 mg q12h subcutaneously	
Abdominal Surgery	n=555 23 (4%)	n=560 16 (3%)	n=560 16 (3%)
Colorectal Surgery	n=673 28 (4%)	n=674 21 (3%)	n=674 21 (3%)

^a 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 and intracranial hemorrhages were always considered major.

Table 3: Major Bleeding Episodes following Hip or Knee Replacement Surgery^a

Indications	Dosing Regimen		Heparin 15,000 U/24h subcutaneously
	Enoxaparin Sodium 40 mg daily subcutaneously	Enoxaparin Sodium 30 mg q12h subcutaneously	
Hip Replacement Surgery without Extended Prophylaxis ^b	n=786 31 (4%)	n=541 32 (6%)	n=541 32 (6%)
Hip Replacement Surgery with Extended Prophylaxis ^b	n=288 4 (2%)	n=221 0 (0%)	n=221 0 (0%)
Knee Replacement Surgery without Extended Prophylaxis ^b	n=294 3 (1%)	n=225 3 (1%)	n=225 3 (1%)

^a 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 and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intracranial hemorrhages were also considered major hemorrhages.

^b Enoxaparin sodium 30 mg every 12 hours subcutaneously initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

^c Enoxaparin sodium 40 mg subcutaneously once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

^d Enoxaparin sodium 40 mg subcutaneously once a day for up to 21 days after discharge.

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

Table 4: Major Bleeding Episodes in Medical Patients with Severely Restricted Mobility during Acute Illness^a

Indication	Dosing Regimen		Placebo ^b
	Enoxaparin Sodium ^c 20 mg daily subcutaneously	Enoxaparin Sodium ^c 40 mg daily subcutaneously	
Medical Patients during Acute Illness	n=351 1 (<1%)	n=360 3 (<1%)	n=362 2 (<1%)

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

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

Table 5: Major Bleeding Episodes in Deep Vein Thrombosis with or without Pulmonary Embolism Treatment^a

Indication	Dosing Regimen		Heparin aPTT Adjusted Intravenous Therapy
	Enoxaparin Sodium 1.5 mg/kg daily subcutaneously	Enoxaparin Sodium 1 mg/kg q12h subcutaneously	
Treatment of DVT and PE	n=298 5 (2%)	n=559 9 (2%)	n=554 9 (2%)

^a 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.

^b 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 enoxaparin sodium or standard heparin therapy and continuing for up to 90 days.

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

Indication	Dosing Regimen		Heparin ^b aPTT Adjusted In
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8.4 Pediatric Use

Safety and effectiveness of enoxaparin sodium in pediatric patients have not been established. Enoxaparin sodium is not approved for use in neonates or infants.

8.5 Geriatric Use

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

Over 2800 patients, 65 years and older, have received enoxaparin sodium in clinical trials. The efficacy of enoxaparin sodium in the geriatric (>65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of enoxaparin sodium were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when enoxaparin sodium was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of enoxaparin sodium-associated bleeding increased with age. Serious adverse events increased with age for patients receiving enoxaparin sodium. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin sodium between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Enoxaparin sodium 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 (2.3) and Clinical Pharmacology (12.3)].

Treatment of Acute ST-Segment Elevation Myocardial Infarction

In the clinical study for treatment of acute ST-segment elevation myocardial infarction, there was no evidence of difference in efficacy between patients >75 years of age (n=1241) and patients less than 75 years of age (n=9015). Patients >75 years of age did not receive a 30 mg intravenous bolus prior to the normal dosage regimen and had their subcutaneous dose adjusted to 0.75 mg/kg every 12 hours [see Dosage and Administration (2.4)]. The incidence of bleeding complications was higher in patients <65 years of age as compared to younger patients (<65 years).

8.6 Patients with Mechanical Prosthetic Heart Valves

The use of enoxaparin sodium injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin sodium injection for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thrombembolism [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 creatinine clearance 30 to <50 mL/min and creatinine clearance 50 to 80 mL/min [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. In patients with renal failure, treatment with enoxaparin sodium injection has been associated with the development of hypotalemia [see Adverse Reactions (6.2)].

8.8 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 per m² concentration) compared to normal-weight patients. Higher exposure for signs and symptoms of bleeding [see Clinical Pharmacology (12.3)].

8.9 Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses of enoxaparin sodium in obese patients (BMI >30 kg/m²) has not been fully determined and there is no consensus for dose adjustment. Observe these patients carefully for signs and symptoms of thromboembolism.

10 OVERDOSAGE

Accidental overdosage following administration of enoxaparin sodium may lead to hemorrhagic complications. Injected enoxaparin sodium may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of enoxaparin sodium injected: 1 mg protamine sulfate should be administered to neutralize 1 mg enoxaparin sodium. 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 may be administered if the aPTT measured 2 to 4 hours after the first infusion. 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 50% neutralization). Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

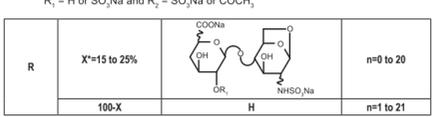
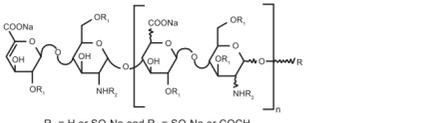
11 DESCRIPTION

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

Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfate-4-heparan sulfate anion and from the non-reducing end and a 2-N,6-O-disulfate-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains a 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 4,500 daltons. The molecular weight distribution is:

<2,000 daltons <20%
2,000 to 8,000 daltons >68%
>8,000 daltons <18%

STRUCTURAL FORMULA



* X = Percent of polysaccharide chain containing 1,6-anhydro derivative on the reducing end
Enoxaparin Sodium Injection, USP 100 mg per mL Concentration contains 10 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1,000 IU/l [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

Enoxaparin Sodium Injection, USP 200 mg per mL Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1,500 IU/l [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.
The Enoxaparin Sodium Injection, USP 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/Storage and Handling (15)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean SD , 14.0±3.1) (based on areas under anti-Factor Xa activity versus time curves) compared to the ratio observed for heparin (mean SD , 1.2±2.0). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose (100 mg/mL concentration), administered subcutaneously every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n=1607). A 30 mg intravenous bolus immediately followed by a 1 mg/kg subcutaneous administration resulted in aPTT postinjection values of 50 seconds. The average aPTT prolongation value on Day 1 was about 16% higher than on Day 4.

12.3 Pharmacokinetics

Pharmacokinetic trials were conducted using the 100 mg/mL formulation. Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcutaneous injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 mg/mL) and 0.38 IU/mL (3.83 mg/mL) after the 20 mg and the 40 mg clinically tested subcutaneous doses, respectively. Mean (n=46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1 mg/kg subcutaneously every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg subcutaneously, based on anti-Factor Xa activity is approximately 100% in healthy subjects. A 30 mg intravenous bolus immediately followed by 1 mg/kg subcutaneously every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 84% of steady-state levels. Steady state is achieved on the second day of treatment. Enoxaparin pharmacokinetics appears to be linear over the recommended dosage ranges [see Dosage and Administration (2)]. After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once-daily regimens in healthy volunteers, the steady state is reached on day 2 with an average exposure about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics. After repeated subcutaneous administration of the 1 mg/kg twice-daily regimen, the steady state is reached from day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range. Although not studied clinically, the 150 mg/mL concentration of enoxaparin sodium is projected to result in anticoagulant activities similar to those of 100 mg/mL and 200 mg/mL concentrations at the same enoxaparin dose. When a daily 1.5 mg/kg subcutaneous injection of enoxaparin sodium was given to 25 healthy male and female subjects using a 100 mg/mL or a 200 mg/mL concentration the following pharmacokinetic profiles were obtained [see Table 13].

Table 13: Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg Subcutaneous Once-Daily Doses of Enoxaparin Sodium Using 100 mg/mL or 200 mg/mL Concentrations

	Concentration	Anti-Xa	Anti-IIa	Hepstat	aPTT
A_{max} (IU/mL or Δ sec)	100 mg/mL	1.37 (±0.23)	0.23 (±0.05)	105 (±17)	19 (±5)
	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	111 (±17)	22 (±7)
$t_{1/2}$ (h)	100 mg/mL	3.2 (2 to 6)	4 (2 to 5)	2.5 (2 to 4.5)	3 (2 to 4.5)
	200 mg/mL	3.5 (2 to 6)	4.5 (2 to 6)	3.3 (2 to 5)	3 (2 to 5)
AUC (SS) (h*IU/mL or h* Δ sec)	100 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)	
	200 mg/mL	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)	

* Means \pm 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 43 L.

Elimination

Following intravenous dosing, the total body clearance of enoxaparin is 26 mL/min. After intravenous dosing of enoxaparin labeled with the gamma-emitter, ¹²⁵I, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after a single subcutaneous dose to about 7 hours after repeated dosing. Significant anti-Factor Xa activity persists in plasma for about 12 hours following a 40 mg subcutaneous once a day dose. Following subcutaneous dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min.

Metabolism

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

Special Populations

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

Geriatric
Apparent clearance and A_{max} derived from anti-Factor Xa values following single and multiple subcutaneous dosing in geriatric subjects were close to those observed in young subjects.

Following once a day subcutaneous dosing of 40 mg enoxaparin, the Day 10 mean anti-Factor Xa activity versus time curve (n=14) was approximately 15% greater than the mean Day 1 AUC value [see Dosage and Administration (2.4)]. This study included patients with heart failure (NYHA Class II or III), acute respiratory failure or complicated chronic respiratory disease (not requiring ventilatory support), acute infection (excluding septic shock), or acute rheumatic disease (acute lumbar or sciatic pain, vertebral compression [due to osteoporosis or tumor], acute arthritic episodes of the lower extremities). A total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged in age from 40 to 87 years (mean

Hepatic Impairment

Studies with enoxaparin sodium injection in patients with hepatic impairment have not been conducted and the impact of hepatic impairment on the exposure to enoxaparin is unknown.

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 to 48 kg/m²) compared to non-obese control subjects, while A_{max} is not increased.

When non-weight-adjusted dosing was administered, it was found after a single-subcutaneous 40 mg dose that anti-Factor Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects [see Use in Specific Populations (8.8)].

Pharmacokinetic Interactions

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 76 mg/m²/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 subcutaneous dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

13.3 Reproductive and Developmental Toxicology

Teratology studies have been conducted in pregnant rats and rabbits at subcutaneous doses of enoxaparin up to 30 mg/kg/day corresponding to 211 mg/m²/day and 410 mg/m²/day in rats and rabbits respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin.

14 CLINICAL STUDIES

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

Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE). In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67 years) with 52.7% men and 47.3% women. Patients were 38% Caucasian, 11% Black, 3.4% Asian and 46.9% unclassified. Enoxaparin sodium 1 mg/kg subcutaneously, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5,000 U every 8 hours subcutaneously in reducing the risk of DVT. The efficacy data are provided below (see Table 14).

Table 14: Efficacy of Enoxaparin Sodium in the Prophylaxis of Deep Vein Thrombosis following Abdominal Surgery

Indication	Dosing Regimen*	
	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Heparin 5,000 U q8h subcutaneously n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures	56 (10.1)	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)

* VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thrombotic in origin
† CI = Confidence Interval

In a second double-blind, parallel group study, enoxaparin sodium 40 mg subcutaneously once a day was compared to heparin 5,000 U every 8 hours subcutaneously in patients undergoing colorectal surgery (n=1047). Enoxaparin at a 1 mg/kg dose (100 mg/mL concentration) was compared to heparin 5,000 U every 8 hours. Patients ranged in age from 18 to 92 years (mean age 50 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 in the Prophylaxis of Deep Vein Thrombosis following Colorectal Surgery

Indication	Dosing Regimen*	
	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Heparin 5,000 U q8h subcutaneously n (%)
All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures	48 (7.1)	45 (6.7)
Total VTE† (%)	48 (7.1) (95% CI: 5 to 9)	45 (6.7) (95% CI: 5 to 9)
DVT Only (%)	47 (7.0) (95% CI: 5 to 9)	44 (6.5) (95% CI: 5 to 8)

* VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thrombotic in origin
† CI = Confidence Interval

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

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

Table 16: Efficacy of Enoxaparin Sodium in the Prophylaxis of Deep Vein Thrombosis following Hip Replacement Surgery

Indication	Dosing Regimen*	
	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)
Treatment Failures	5 (10)*	23 (46)
Total DVT (%)	5 (10) (95% CI: 5 to 19)	23 (46) (95% CI: 35 to 55)
Proximal DVT (%)	1 (2)	11 (22)

* p value versus placebo = 0.0002
† p value versus placebo = 0.0134

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

Table 17: Efficacy of Enoxaparin Sodium in the Prophylaxis of Deep Vein Thrombosis following Hip Replacement Surgery

Indication	Dosing Regimen*		
	10 mg daily subcutaneously n (%)	30 mg q12h subcutaneously n (%)	40 mg daily subcutaneously n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)
Treatment Failures	16 (10)	12 (6)	12 (6)
Total DVT (%)	40 (25) (95% CI: 19 to 47)	22 (11)* (95% CI: 6 to 18)	27 (14) (95% CI: 9 to 21)
Proximal DVT (%)	17 (11)	8 (4)†	9 (5)

* p value versus enoxaparin sodium 10 mg once a day = 0.0008
† p value versus enoxaparin sodium 10 mg once a day = 0.0168

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens. In a double-blind study, enoxaparin sodium 30 mg every 12 hours subcutaneously was compared to placebo in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the study and 131 patients were treated. The mean age was 62 years. Patients were 93% Caucasian, 6% Black, <1% Asian, and 1% others. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The efficacy data are provided below (see Table 18).

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

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

* p value versus placebo = 0.0001
† CI = Confidence Interval

† p value versus placebo = 0.013

‡ CI = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium 30 mg every 12 hours subcutaneously in patients undergoing elective knee replacement surgery was compared to heparin 5,000 U every 8 hours subcutaneously. A total of 453 patients were randomized in the study and all patients were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.6% others. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was lower for enoxaparin sodium 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 40 mg subcutaneously, initiated up to 12 hours prior to surgery for the prophylaxis of postoperative DVT. At the end of the peri-operative period, all patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin sodium 40 mg (n=90) once a day subcutaneously or to placebo (n=89) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 68.4 years) with 43.7% men and 56.3% women. Similar to the first study the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo, with a statistically significant difference in both total DVT (enoxaparin sodium 21 [16%] versus placebo 45 [24%]; p<0.001) and proximal DVT (enoxaparin sodium 8 [8%] versus placebo 28 [21%]; p<0.001).

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

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

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

† p value versus placebo = 0.537

In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin sodium 40 mg subcutaneously, initiated up to 12 hours prior to surgery. All patients were examined for clinical signs and symptoms of venous thromboembolism (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 40 mg (n=131) once a day subcutaneously or to placebo (n=131) for 3 weeks. A total of 262 patients were randomized in the study double-blind phase and all patients were treated. Patients ranged in age from 44 to 87 years (mean age 68.5 years) with 43.1% men and 56.9% women. Similar to the first study the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo, with a statistically significant difference in both total DVT (enoxaparin sodium 21 [16%] versus placebo 45 [34%]; p<0.001) and proximal DVT (enoxaparin sodium 8 [8%] 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 20 mg or 40 mg once a day subcutaneously was compared to placebo in the prophylaxis of deep vein thrombosis (DVT) in medical patients with severely restricted mobility during acute illness (defined as walking distance of <10 meters for <3 days). This study included patients with heart failure (NYHA Class II or III), acute respiratory failure or complicated chronic respiratory disease (not requiring ventilatory support), acute infection (excluding septic shock), or acute rheumatic disease (acute lumbar or sciatic pain, vertebral compression [due to osteoporosis or tumor], acute arthritic episodes of the lower extremities). A total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged in age from 40 to 87 years (mean

age 73 years) with equal proportions of men and women. Treatment continued for a maximum of 14 days. Similar to the first study, when given at a dose of 40 mg once a day subcutaneously, enoxaparin sodium 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 in the Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility during Acute Illness

Indication	Dosing Regimen*		
	Enoxaparin Sodium 20 mg daily subcutaneously n (%)	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Placebo n (%)
All Treated Medical Patients during Acute Illness	351 (100)	360 (100)	362 (100)
Treatment Failure†	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)

INSTRUCTIONS FOR USE
ENOXAPARIN SODIUM (ee nox" a par' in soe' dee um) INJECTION
for subcutaneous use

Single-dose prefilled syringe

This Instructions for Use contains information on how to prepare and inject Enoxaparin Sodium Injection prefilled syringe.

Read this Instructions for Use before using the Enoxaparin Sodium Injection prefilled syringe and each time you get a new prescription. There may be new information. **Do not inject yourself or someone else until you have been shown how to inject Enoxaparin Sodium Injection.** Your healthcare provider can show you or your caregiver how to prepare and inject a dose of Enoxaparin Sodium Injection. Call your healthcare provider if you have any questions.

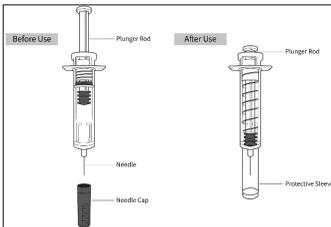
Important information:

- Your healthcare provider will tell you the prescribed dose that you should take and how often you will need to inject Enoxaparin Sodium Injection. If your dose is based on your body weight, your dose of Enoxaparin Sodium Injection might be less than what is in the prefilled syringe.
- Enoxaparin Sodium Injection is injected as a subcutaneous (under the skin) injection only. **Do not inject Enoxaparin Sodium Injection into muscle.**
- Do not use the Enoxaparin Sodium Injection prefilled syringe if the needle cap is missing or not securely attached.**
- Do not remove the needle cap until just before you give the injection.**
- Do not touch the syringe plunger rod until you are ready to inject. Do not pull back on the plunger rod at any time.**
- Do not get rid of any air bubble(s) in the Enoxaparin Sodium Injection prefilled syringe.** This can lead to a loss of the medicine.
- To avoid bruising, **do not rub** the injection site after you have injected yourself.
- To protect from needle-stick injuries, each prefilled syringe has a safety system that covers the needle after injection.
- Throw away (dispose of) the used Enoxaparin Sodium Injection prefilled syringe and needle cap right after use, even if there is medicine left in the prefilled syringe. See **Step 13: Dispose of used Enoxaparin Sodium Injection prefilled syringes and needle caps** below.
- Enoxaparin Sodium Injection is for one time use only. **Do not reuse an Enoxaparin Sodium Injection prefilled syringe.**

Storing Enoxaparin Sodium Injection prefilled syringes:

- Store Enoxaparin Sodium Injection prefilled syringes at 77°F (25°C).
- Store Enoxaparin Sodium Injection prefilled syringes in the original carton or packaging until ready to use.
- Keep Enoxaparin Sodium Injection and all medicines out of the reach of children.**

Parts of Enoxaparin Sodium Injection prefilled syringe:



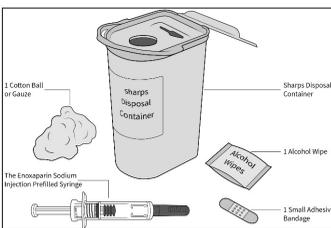
Preparing to inject Enoxaparin Sodium Injection:

Step 1: Gather the following supplies for your injection (see Figure A):

- 1 Enoxaparin Sodium Injection prefilled syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a small adhesive bandage, if needed*
- a sharps disposal container* (see Step 13)

*Items not included.

Figure A



Step 2: Wash your hands well with soap and water.

Step 3: Preparing a dose of Enoxaparin Sodium Injection

Take the prefilled syringe out of the package.

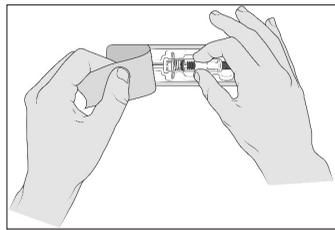
Open the packaging by peeling the lid at the arrow as directed.

Take the prefilled syringe out of the plastic container by holding the middle of the syringe body (see Figure B).

- Do not remove the prefilled syringe by pulling on the plunger rod or the needle cap as this may damage the syringe.**
- Do not pull off the needle cap until you are ready to inject.**

- Do not use the Enoxaparin Sodium Injection prefilled syringe if it has been dropped on a hard surface or damaged.**

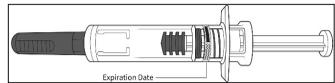
Figure B



Step 4: Check the Enoxaparin Sodium Injection prefilled syringe

- When you receive your Enoxaparin Sodium Injection syringes, always check to see that:
 - you have the correct medicine and dose.
 - the expiration date on the prefilled syringe has not passed (see Figure C).
- Do not use the Enoxaparin Sodium Injection prefilled syringe if the expiration date has passed.**

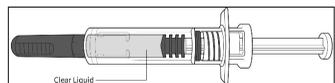
Figure C



Step 5: Check the medicine

- Look at the medicine inside the Enoxaparin Sodium Injection prefilled syringe:
 - The liquid should be clear and colorless or light yellow (see Figure D).
 - Note:** You may see air bubble(s), this is normal. Do not try to remove any air bubbles.
- Do not use the Enoxaparin Sodium Injection prefilled syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.**

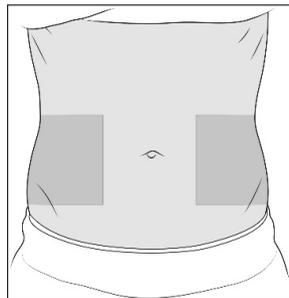
Figure D



Step 6: Choose your injection site

- You can inject into either the right or left side of your stomach area (abdomen), at least 2 inches away from your belly button and out towards your side (see Figure E).
- You should alternate between the left or right side of your stomach each time you give yourself an injection.
- Do not inject into skin that has bruises or scars.**
- Do not inject through clothes.**

Figure E

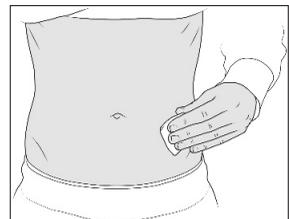


Step 7: Clean the injection site

Clean the injection site with an alcohol wipe (see Figure F).

Let your skin dry before injecting.

Figure F

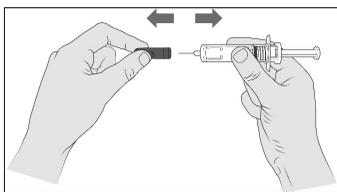


Step 8: Remove the needle cap

Hold the prefilled syringe in the middle of the body with the needle pointing away from you. Remove the needle cap by pulling it straight off the syringe (see Figure G).

- Do not twist the needle cap to avoid bending the needle.**
- Do not put the needle cap back on.**
- Do not touch the needle.**

Figure G

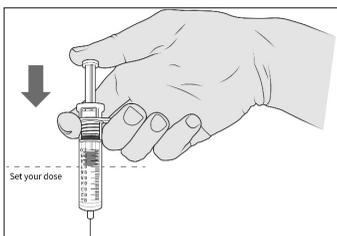


Step 9: Injecting a dose that is less than the full amount in the prefilled syringe. If your prescribed dose is the same as the amount in the prefilled syringe, go to Step 10.

If your dose is based on your bodyweight, your healthcare provider may prescribe less than the full amount in the syringe. You will have to get rid of (discard) some of the medicine from the prefilled syringe before you inject Enoxaparin Sodium Injection.

To measure your prescribed dose, hold the prefilled syringe with the needle pointing down. Carefully watch the numbers on the syringe as you push the plunger down until the amount left in the syringe is the same as your prescribed dose. The tip of the plunger should line up with the number for your prescribed dose (see Figure H).

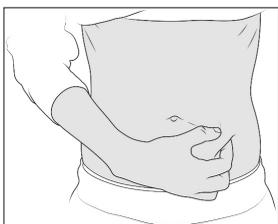
Figure H



Step 10: Injecting Enoxaparin Sodium Injection

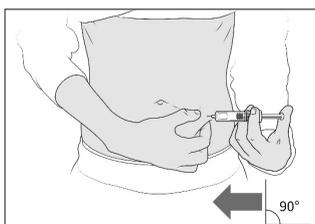
Hold the prefilled syringe like a pencil in your hand with the needle pointing down. With your other hand, pinch the cleaned stomach (abdomen) area between your forefinger and thumb to make a fold in the skin (see Figure I). Make sure you hold the skin fold during the entire injection.

Figure I



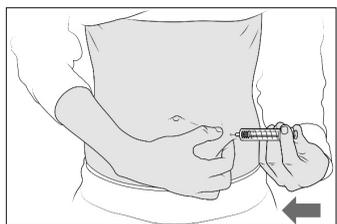
Insert the full length of the needle straight into the skin fold at about a 90° angle (see Figure J).

Figure J



Push the plunger rod down slowly and steadily with your thumb until the Enoxaparin Sodium Injection prefilled syringe is empty (see Figure K).

Figure K

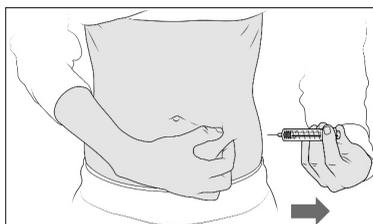


Step 11: Remove the needle

Remove the needle from the injection site by pulling it straight out while keeping your fingers on the plunger rod (see Figure L).

- Do not put the needle cap back on.
- Do not rub your skin after the injection.

Figure L

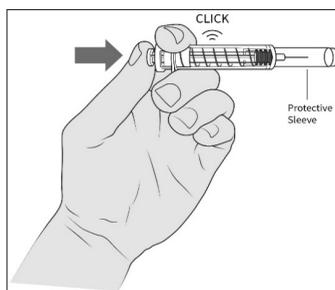


Step 12: Activate the safety system

Point the needle away from yourself and other people, and firmly push the plunger rod again to activate the safety system. The protective sleeve will automatically come down and cover the needle. You will hear a "click" when the protective sleeve is released (see Figure M).

- You will feel some resistance. This is normal. Keep pushing until you hear the "click."
- The safety system can only be activated after the syringe has been emptied.
- Only activate the safety system after you have removed the needle from your skin.
- Activation of the safety system may cause a small amount of liquid to leak out of the syringe. Activate the system while facing the syringe away from yourself and other people.

Figure M



Step 13: Dispose of used Enoxaparin Sodium Injection prefilled syringes and needle caps

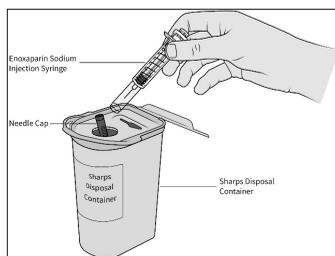
Put the used Enoxaparin Sodium Injection prefilled syringe and needle cap in an FDA-cleared sharps disposal container right away after use (see Figure N). Do not dispose of Enoxaparin Sodium Injection prefilled syringes or needle caps in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at <http://www.fda.gov/safesharpsdisposal>.

Figure N



meitheal
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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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