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

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 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 is a low molecular weight heparin (LMWH) indicated for:

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

Dosage and Administration

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Active major bleeding (4)
- History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (4)
- Hypersensitivity to enoxaparin sodium (4)
- Hypersensitivity to heparin or pork products (4)
- Hypersensitivity to benzyl alcohol (for multiple-dose formulation only) (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, diaphoresis, nausea, ecchymosis, fever, edema, peripheral edema, dyspnea, and injection site pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 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. (8.9)

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

Revised: 12/2021

5.8 Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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8.5 Patients with Mechanical Prosthetic Heart Valves

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10 OVERDOSAGE

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12 CLINICAL PHARMACOLOGY

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12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

13.3 Reproductive and Developmental Toxicology

14 CLINICAL STUDIES

14.1 Prophylaxis of Deep Vein Thrombosis following Abdominal Surgery in Patients at Risk for Thromboembolic Complications
1. INDICATIONS AND USAGE

1.1 Prophylaxis of Deep Vein Thrombosis

Enoxaparin sodium 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 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 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, 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 fibrinolytic therapy.

2. DOSAGE AND ADMINISTRATION

2.1 Pretreatment Evaluation

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

2.2 Adult Dosage

2.2.1 Abdominal Surgery

The recommended dose of enoxaparin sodium 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)].

2.2.2 Hip or Knee Replacement Surgery

The recommended dose of enoxaparin sodium 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 of 40 mg once a day subcutaneously may be considered for hip replacement surgery for up to 3 weeks. Administer the initial dose 12 to 36 hours prior to surgery.
Table 1: Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30 mL/minute) (continued)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, when administered in conjunction with aspirin</td>
<td>1 mg/kg administered subcutaneously once daily (no initial bolus)</td>
</tr>
</tbody>
</table>

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 by intramuscular injection.

Administer enoxaparin sodium 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.

Use a tuberculin syringe or equivalent when using enoxaparin sodium multiple-dose vials to assure 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 administration by deep subcutaneous injection.
- Do not expel the air bubble from the prefilled syringes before the injection, to avoid the loss of drug.
- Do not inject into skin that has bruises or scars. Do not inject through clothes.
- 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 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 packaging by peeling at the arrow as directed on the lid. Do not remove by pulling on the plunger as this may damage the syringe.
- 1. Remove the needle shield by pulling it straight off the syringe (see Figure A). If less than the full volume syringe is needed to administer the prescribed dose, eject syringe contents until the prescribed dose is left in the syringe.

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

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

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

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 through an intravenous line. Do not mix or coadminister enoxaparin sodium 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 to prevent mixing of drugs. Enoxaparin sodium is compatible with normal saline solution (0.9%) or 5% dextrose in water.

2.6 Monitoring for Safety

During therapy 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.

If during enoxaparin sodium therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of enoxaparin sodium [see Clinical Pharmacology (12.3)].

Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are not adequate for monitoring the anticoagulant effects of enoxaparin sodium.

3 DOSAGE FORMS AND STRENGTHS

Enoxaparin sodium injection is a clear, colorless to pale-yellow solution available in two concentrations.

- 100 mg/mL Concentration
  - Single-Dose Prefilled Syringes: 30 mg/0.3 mL, 40 mg/0.4 mL
  - Single-Dose Graduated: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL
- 150 mg/mL Concentration
  - Single-Dose Graduated: 120 mg/0.8 mL, 150 mg/1 mL

4 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)]
5.5 Thrombocytopenia
Thrombocytopenia can occur with the administration of enoxaparin sodium. Moderate thrombocytopenia (platelet counts between 100,000/mm$^3$ and 50,000/mm$^3$) 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/mm$^3$ 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/mm$^3$, 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-fIIa 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 (6 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 adjusting of dosage may be needed [see Use in Specific Populations (8.6)].

5.8 Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative
Enoxaparin sodium multiple-dose vials are not approved for use in neonates or infants. Serious and fatal adverse reactions including “gassing syndrome” can occur in neonates and low-birth-weight infants treated with benzyl alcohol-preserved drugs, including enoxaparin sodium multiple-dose vials. The “gassing syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known [enoxaparin sodium multiple-dose vials contain 15 mg of benzyl alcohol per mL] [see Use in Specific Populations (8.4)]. Because benzyl alcohol may cross the placenta, if anticoagulation with enoxaparin sodium is needed during pregnancy, use the preservative-free formulations where possible [see Use in Specific Populations (8.1)].

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, 1,388 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 varied from 40 mg subcubtaneously once daily to 30 mg subcubtaneously twice daily. In the clinical studies for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction doses were 1 mg/kg every 12 hours and in the clinical studies for treatment of acute ST-elevation myocardial infarction doses were 30 mg intravenous bolus followed by 1 mg/kg every 12 hours subcubtaneously.

Hemorrhage
Severe and fatal bleeding 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

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dosing Regimen</th>
<th>Enoxaparin Sodium (mg)</th>
<th>Heparin (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40 mg daily subcubtaneously</td>
<td>5,000 U q8h subcubtaneously</td>
</tr>
<tr>
<td>Abdominal Surgery</td>
<td>n=555</td>
<td>23 (4%)</td>
<td>16 (3%)</td>
</tr>
<tr>
<td></td>
<td>n=560</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal Surgery</td>
<td>n=673</td>
<td>28 (4%)</td>
<td>21 (3%)</td>
</tr>
<tr>
<td></td>
<td>n=674</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 intrachrinal hemorrhages were always considered major.
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.

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

‡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.

§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 prophylactic regimens compared in clinical trials. Injection site hemorrhages 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 3: Major Bleeding Episodes in Medical Patients with Severely Restricted Mobility during Acute Illness

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dosing Regimen</th>
<th>Enoxaparin Sodium</th>
<th>Enoxaparin Sodium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Patients during Acute Illness</td>
<td></td>
<td>20 mg daily</td>
<td>40 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>subcutaneously</td>
<td>subcutaneously</td>
<td></td>
</tr>
<tr>
<td>n=351</td>
<td>n=360</td>
<td>1 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>n=362</td>
<td>n=362</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Major Bleeding Episodes in Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dosing Regimen</th>
<th>Enoxaparin Sodium</th>
<th>Enoxaparin Sodium</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Replacement Surgery without Extended Prophylaxis</td>
<td>-</td>
<td>n=786</td>
<td>31 (4%)</td>
<td>n=541</td>
</tr>
<tr>
<td>Hip Replacement Surgery with Extended Prophylaxis</td>
<td>-</td>
<td>n=388</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>Peri-operative Period</td>
<td>n=221</td>
<td>0 (0%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Extended Prophylaxis Period</td>
<td>n=221</td>
<td>1 (%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Knee Replacement Surgery without Extended Prophylaxis</td>
<td>-</td>
<td>n=294</td>
<td>3 (1%)</td>
<td>n=225</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dosing Regimen</th>
<th>Enoxaparin Sodium</th>
<th>Enoxaparin Sodium</th>
<th>Heparin aPTT Adjusted Intravenous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of DVT and PE</td>
<td>n=298</td>
<td>5 (2%)</td>
<td>9 (2%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td></td>
<td>n=559</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=554</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Enoxaparin Sodium</th>
<th>Heparin aPTT Adjusted Intravenous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable Angina and Non-Q-Wave MI</td>
<td>n=1578</td>
<td>17 (1%)</td>
<td>18 (1%)</td>
</tr>
</tbody>
</table>

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

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

‡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. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

### Table 7: Major Bleeding Episodes in Acute ST-Segment Elevation Myocardial Infarction

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Enoxaparin Sodium</th>
<th>Heparin aPTT Adjusted Intravenous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ST-Segment Elevation Myocardial Infarction</td>
<td>n=10176</td>
<td>211 (2.1)</td>
<td>138 (1.4)</td>
</tr>
<tr>
<td>Major bleeding (including ICH)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhages (ICH)</td>
<td>84 (0.8)</td>
<td></td>
<td>66 (0.7)</td>
</tr>
</tbody>
</table>

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

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

Elevations of Serum Aminotransferases

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

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

Local Reactions

Local irritation, pain, hematoma, ecchymosis, and erythema may follow subcutaneous injection of enoxaparin sodium.

Adverse Reactions in Patients Receiving Enoxaparin Sodium for Prophylaxis or Treatment of DVT, PE Other adverse reactions that were thought to be possibly or probably related to treatment with enoxaparin sodium, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the enoxaparin sodium group, are provided below (see Tables 8 to 11).

### Table 8: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium–Treated Patients Undergoing Abdominal or Colorectal Surgery

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Enoxaparin Sodium</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 mg daily</td>
<td>5000 U q24h</td>
</tr>
<tr>
<td></td>
<td>subcutaneously</td>
<td>subcutaneously</td>
</tr>
<tr>
<td></td>
<td>n=1228</td>
<td>n=1234</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>&lt;1</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

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 9: Adverse Reactions Occurring at \(\geq 2\%\) Incidence in Enoxaparin Sodium–Treated Patients Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Enoxaparin Sodium 40 mg daily subcutaneously</th>
<th>Placebo</th>
<th>Enoxaparin Sodium 30 mg q12h subcutaneously</th>
<th>Placebo</th>
<th>Heparin 15,000 U q24h subcutaneously</th>
<th>Placebo</th>
<th>Placebo q12h subcutaneously</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-operative Period</td>
<td>n=288</td>
<td>n=131</td>
<td>n=1080</td>
<td>n=766</td>
<td>n=115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Total</td>
<td>Severe</td>
<td>Total</td>
<td>Severe</td>
<td>Total</td>
<td>Severe</td>
<td>Total</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>5</td>
<td>&lt;1</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>&lt;1</td>
<td>13</td>
<td>0</td>
<td>5</td>
<td>&lt;1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>&lt;2</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>&lt;1</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Data represent enoxaparin sodium 40 mg subcutaneously once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received enoxaparin sodium peri-operatively in an unblinded fashion in one clinical trial.

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

### Table 10: Adverse Reactions Occurring at \(\geq 2\%\) Incidence in Enoxaparin Sodium–Treated Medical Patients with Severely Restricted Mobility during Acute Illness

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Enoxaparin Sodium 40 mg daily subcutaneously n=360</th>
<th>Placebo subcutaneously n=382</th>
<th>Enoxaparin Sodium 1 mg/kg q12h subcutaneously n=559</th>
<th>Placebo</th>
<th>Heparin aPTT Adjusted Intravenous Therapy n=544</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Total</td>
<td>Severe</td>
<td>Total</td>
<td>Severe</td>
<td>Total</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.3</td>
<td>5.2</td>
<td>2.8</td>
<td>2.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.5</td>
<td>1.7</td>
<td>2.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

### Table 11: Adverse Reactions Occurring at \(\geq 2\%\) Incidence in Enoxaparin Sodium–Treated Patients Undergoing Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Enoxaparin Sodium 1.3 mg/kg daily subcutaneously n=298</th>
<th>Placebo</th>
<th>Enoxaparin Sodium 1 mg/kg q12h subcutaneously n=559</th>
<th>Placebo</th>
<th>Heparin aPTT Adjusted Intravenous Therapy n=544</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Total</td>
<td>Severe</td>
<td>Total</td>
<td>Severe</td>
<td>Total</td>
</tr>
<tr>
<td>Injection Site Hemorrhage</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

**Table 12: Serious Adverse Events Occurring at \(\geq 0.5\%\) Incidence in Enoxaparin Sodium–Treated Patients with Unstable Angina or Non-Q-Wave Myocardial Infarction**

- **Adverse Reactions in Enoxaparin Sodium–Treated Patients with Acute ST-Segment Elevation Myocardial Infarction**
  - In a clinical trial in patients with acute ST-segment elevation myocardial infarction, thrombocytopenia occurred at a rate of 1.5%.

### Postmarketing Experience

The following adverse reactions have been identified during postapproval use of enoxaparin sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. There have been reports of epidual or spinal hematoma formation with concurrent use of enoxaparin sodium and spinal/epidural anesthesia or spinal puncture. The majority of patients had a postoperative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Local reactions at the injection site (e.g., nodules, inflammation, oozing), systemic allergic reactions (e.g., urticaria, anaphylactic/anaphylactoid reactions including shock), vesiculobullous rash, cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thrombocytopenia with thrombosis [see Warnings and Precautions (5.5)] have been reported. Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues). Very rare cases of hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

### 7 DRUG INTERACTIONS

Whenever possible, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of enoxaparin sodium therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), diuretics, or sulfonpyrazone. If coadministration is essential, conduct close clinical and laboratory monitoring [see Warnings and Precautions (5.1)].

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Risk Summary

Placental transfer of enoxaparin was observed in the animal studies. Human data from a retrospective cohort study, which included 693 live births, suggest that enoxaparin does not increase the risk of major
Developmental abnormalities (see Data). Based on animal data, enoxaparin is not predicted to increase the risk of major developmental abnormalities (see Data). 

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thrombembolic disorders and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see Warnings and Precautions (5.7) and Use in Specific Populations (8.6)]. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

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

It is not known if monitoring of anti-Factor Xa activity and dose adjustment (by weight or anti-Factor Xa activity) of enoxaparin sodium affect the safety and the efficacy of the drug during pregnancy. Cases of "gassing syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of enoxaparin sodium contains 15 mg benzyl alcohol per 1 mL as a preservative [see Warnings and Precautions (5.8)].

Data

Human data

There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewing the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received enoxaparin sodium. Causally for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases. A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been conducted [see Warnings and Precautions (5.7)].

Animal data

Teratology studies have been conducted in pregnant rats and rabbits at subcutaneous doses of enoxaparin sodium up to 5 times the recommended human dose (by comparison with 2 mg/kg as the maximum recommended daily dose). There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Lactation

Risk Summary

It is unknown whether enoxaparin sodium is excreted in human milk. In lactating rats, the passage of enoxaparin sodium and 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.

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

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

8.5 Geriatric Use

Enoxaparin sodium is not approved for use in neonates or infants.

8.6 Patients with Mechanical Prosthetic Heart Vessels

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. Enoxaparin sodium does not bind to protein and is partially cleared by the liver. After intravenous administration, protamine competes with enoxaparin sodium for binding sites on Factor Xa and rapidly neutralizes the anticoagulant activity of enoxaparin sodium in plasma. The dose of protamine required is calculated using the aPTT. When the aPTT is shorter than the aPTT for controls, additional protamine is not required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

11 DESCRIPTION

Enoxaparin sodium injection is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin. The pH of the injection is 5.5 to 7.5. Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group and a non-reducing end and a 2-N-O-sulfoo-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 of 2000 to 8000 daltons. The weight average molecular weight is about 4500 daltons. The molecular weight distribution is: <2000 daltons <20% 2000 to 8000 daltons ≥88% >8000 daltons ≥18%
Absorption

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

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

The enoxaparin sodium prefilled syringes and graduated prefills are preservative-free and intended for use only as a single-dose injection. The multiple-dose vial contains 15 mg benzyl alcohol per 1 mL as a preservative [see Dosage and Administration (2) and How Supplied/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 llia 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).

In clinical studies in normal weight patients, peak anti-Factor Xa activity occurred within 1 hour (tmax) after subcutaneous administration of 100 mg/mL concentrations and within 2 hours (tmax) after subcutaneous administration of 150 mg/mL concentrations. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg dose, was approximately 50% to 60% (n=16) compared to the label 52% to 62% (n=16) reported for enoxaparin sodium injection 100 mg/mL Concentration. Pharmacokinetic analysis of data from all studies showed that bioavailability was greater for 200 mg/mL than 100 mg/mL concentrations.

In several clinical studies, absorption of enoxaparin sodium was determined by gamma-emission and/or high-performance liquid chromatography. After subcutaneous administration of labeled enoxaparin sodium, peak activity was observed about 2 hours. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg dose, was 52% to 62% (n=16) compared to the label 50% to 60% (n=16) reported for enoxaparin sodium injection 100 mg/mL Concentration.

Pharmacokinetic Interaction

Following intravenous dosing of enoxaparin labeled with the gamma-emitter, 131I, 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.

Mean initial peak anti-Factor Xa activity was 1.16 IU/mL (n=16) and average exposure corresponding to 84% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

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

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Anti-Xa</th>
<th>Anti-IIa</th>
<th>Heptest</th>
<th>aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/mL</td>
<td>1.37±(0.23)</td>
<td>0.23±(0.05)</td>
<td>105±(17)</td>
<td>19±(5)</td>
</tr>
<tr>
<td>200 mg/mL</td>
<td>1.45±(0.22)</td>
<td>0.26±(0.05)</td>
<td>111±(17)</td>
<td>22±(7)</td>
</tr>
<tr>
<td>90% CI</td>
<td>102%–110%</td>
<td>102%–111%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td>3 (2–6)</td>
<td>4 (2–5)</td>
<td>2.5 (2–4.5)</td>
<td>3 (2–4.5)</td>
</tr>
<tr>
<td>AUC (ss) (h IU/mL or h* IU/mL)</td>
<td>14.26±(2.83)</td>
<td>1.54±(0.61)</td>
<td>1321±(219)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>90% CI</td>
<td>105%–112%</td>
<td>103%–109%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

†Median (range)

Distribution

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

Elimination

Following intravenous dosing, the total body clearance of enoxaparin is 26 mL/min. After intravenous dosing of enoxaparin labeled with the gamma-emitter, 131I, 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

Apparent clearance and Amax 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 Amax derived from anti-Factor Xa values following single and multiple subcutaneous dosing in geriatric subjects were close to those observed in young subjects. Following once a day subcutaneous dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value [see Dosage and Administration (2.4) and Use in Specific Populations (8.5)].

Renal impairment

A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady state, is marginally increased in patients with creatinine clearance 50 to 80 mL/min and patients with creatinine clearance 30 to <50 mL/min 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 30–48 kg/m2) compared to non-obese control subjects, while Amax 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 in 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 78 mg/m²/day.

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 motority, 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 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 5000 U every 8 hours subcutaneously in reducing the risk of DVT. The efficacy data are provided below (see Table 14).

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin Sodium 40 mg daily subcutaneously n (%)</td>
</tr>
<tr>
<td>All Treated Abdominal Surgery Patients</td>
<td>555 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total VTE (%)</td>
<td>56 (10.1)</td>
</tr>
<tr>
<td>(95% CI: 8 to 13)</td>
<td>(95% CI: 9 to 14)</td>
</tr>
<tr>
<td>DVT Only (%)</td>
<td>54 (9.7)</td>
</tr>
<tr>
<td>(95% CI: 7 to 12)</td>
<td>(95% CI: 8 to 13)</td>
</tr>
</tbody>
</table>

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

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

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

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin Sodium 40 mg daily subcutaneously n (%)</td>
</tr>
<tr>
<td>All Treated Colorectal Surgery Patients</td>
<td>673 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total VTE (%)</td>
<td>48 (7.1)</td>
</tr>
<tr>
<td>(95% CI: 5 to 9)</td>
<td>(95% CI: 5 to 9)</td>
</tr>
<tr>
<td>DVT Only (%)</td>
<td>47 (7.0)</td>
</tr>
<tr>
<td>(95% CI: 5 to 9)</td>
<td>(95% CI: 5 to 8)</td>
</tr>
</tbody>
</table>

*p value versus enoxaparin sodium 10 mg once a day = 0.0001
†CI = Confidence Interval
‡p value versus enoxaparin sodium 10 mg once a day = 0.013
§CL = Confidence Limit

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin Sodium 30 mg q12h subcutaneously n (%)</td>
</tr>
<tr>
<td>All Treated Hip Replacement Patients</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total DVT (%)</td>
<td>5 (10)†</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>1 (2)‡</td>
</tr>
</tbody>
</table>

*p value versus placebo = 0.0002
†p value versus placebo = 0.013

A double-blind, multicenter study compared three dosing regimens of enoxaparin sodium in patients with hip replacement. A total of 372 patients were randomized in the study and 568 patients were treated. Patients ranged in age from 31 to 88 years (mean age 64.7 years) with 63% men and 37% women. Patients were 98% 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin Sodium 10 mg daily subcutaneously n (%)</td>
</tr>
<tr>
<td>All Treated Hip Replacement Patients</td>
<td>161 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total DVT (%)</td>
<td>40 (25)†</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>17 (11)†</td>
</tr>
</tbody>
</table>

*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, of which 99 had total knee replacement and 32 had either unicompartamental knee replacement or tibial osteotomy. The 99 patients with total knee replacement ranged in age from 42 to 85 years (mean age 70.2 years) with 36.4% men and 63.6% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued up to 15 days after surgery. The incidence of proximal and total DVT after surgery was significantly lower for 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 Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin Sodium 30 mg q12h subcutaneously n (%)</td>
</tr>
<tr>
<td>All Treated Knee Replacement Patients</td>
<td>47 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total DVT (%)</td>
<td>5 (11)†</td>
</tr>
<tr>
<td>(95% CI: 1 to 21)</td>
<td>(95% CI: 47 to 76)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>0 (0)‡</td>
</tr>
</tbody>
</table>

*p value versus placebo = 0.0001
†CI = Confidence Interval
‡p value versus placebo = 0.013
§CL = Confidence Limit
Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium 30 mg every 12 hours subcutaneously in patients undergoing elective knee replacement surgery was compared to heparin 5000 U every 8 hours subcutaneously. A total of 453 patients were randomized in the study and all were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.6% others. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was lower for 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 69.4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo. The efficacy data are provided below (see Table 19).

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

<table>
<thead>
<tr>
<th>Indication (Post Discharge)</th>
<th>Post-discharge Dosing Regimen</th>
<th>Placebo Daily subcutaneously n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated Extended Prophylaxis Patients</td>
<td>Enoxaparin Sodium</td>
<td>90 (100)</td>
</tr>
<tr>
<td>Treatment Failures</td>
<td>Total DVT (%)</td>
<td>(95% CI: 6 to 14)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>6 (7)</td>
<td>(95% CI: 2 to 13)</td>
</tr>
</tbody>
</table>

*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 thromboembolic (VTE) disease. In a double-blind design, patients without clinical signs and symptoms of VTE disease were randomized to a post-discharge regimen of either enoxaparin sodium 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 56.3% 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% [95% CI: 16% to 26%]) and proximal DVT (enoxaparin sodium 8% [95% CI: 4% to 14%]) versus placebo. The efficacy data are provided below (see Table 19).

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated Medical Patients during Acute Illness</td>
<td>Enoxaparin Sodium 40 mg daily subcutaneously n (%)</td>
</tr>
<tr>
<td>Treatment Failure Total VTE (%)</td>
<td>43 (12.3)</td>
</tr>
</tbody>
</table>

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

14.4 Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

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

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated DVT Patients with or without PE</td>
<td>Enoxaparin Sodium 1.5 mg/kg daily subcutaneously n (%)</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>Total VTE (%)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>9 (2.9)</td>
</tr>
</tbody>
</table>

*p value versus placebo = 0.001
†CI = Confidence Interval
‡p value versus placebo = 0.537

Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT were randomized to enoxaparin sodium or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outpatient exclusion criteria included the following: inability to receive outpatient heparin therapy because of associated comorbid conditions or potential for non-compliance and inability to attend follow-up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but only enoxaparin sodium enoxaparin sodium once a day versus heparin (3.0 to 3.5) | Enoxaparin sodium every 12 hours versus heparin (4.2 to 1.7)
In a multicenter, double-blind, parallel group study, patients who recently experienced unstable angina or non-Q-wave myocardial infarction were randomized to either enoxaparin sodium 1 mg/kg every 12 hours subcutaneously or heparin intravenous bolus (5000 U) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study,* and 100% were male. Racial distribution was: 70% Caucasian, 9.8% Asian, 0.2% Black, and 2.8% other. Medical history included smoking among 35% of patients and hypertension among 26%. The MI at entry was anterior in 43%, non-anterior in 56%, and both in 1%. The primary efficacy endpoint was the composite of death from any cause or myocardial re-infarction at any time during the first 30 days after randomization. Total follow-up was one year.

The rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, 6.3% compared to 8.2% at 30 days (p=0.047).

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

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

In a multicenter, double-blind, parallel group study, patients who recently experienced unstable angina or non-Q-wave myocardial infarction were randomized to either enoxaparin sodium 1 mg/kg every 12 hours subcutaneously or heparin intravenous bolus (5000 U) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study,* and 100% were male. Racial distribution was: 70% Caucasian, 9.8% Asian, 0.2% Black, and 2.8% other. Medical history included smoking among 35% of patients and hypertension among 26%. The MI at entry was anterior in 43%, non-anterior in 56%, and both in 1%. The primary efficacy endpoint was the composite of death from any cause or myocardial re-infarction at any time during the first 30 days after randomization. Total follow-up was one year.

The rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, 6.3% compared to 8.2% at 30 days (p=0.047).

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

The rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, and 12% in the unfractionated heparin group, a 17% reduction in the relative risk, (P=0.000003) (see Table 23).

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

The rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, and 12% in the unfractionated heparin group, a 17% reduction in the relative risk, (P=0.000003) (see Table 23).

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

The rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, and 12% in the unfractionated heparin group, a 17% reduction in the relative risk, (P=0.000003) (see Table 23).
Table 25: Efficacy of Enoxaparin Sodium in the Treatment of Acute ST-Segment Elevation Myocardial Infarction (continued)

<table>
<thead>
<tr>
<th>Outcome at 8 Days</th>
<th>Enoxaparin (N=10,256)</th>
<th>UFH (N=10,223)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Myocardial Re-infarction</td>
<td>740 (7.2)</td>
<td>954 (9.3)</td>
<td>0.77 (0.71 to 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>559 (5.5)</td>
<td>605 (5.9)</td>
<td>0.92 (0.82 to 1.03)</td>
<td>0.15</td>
</tr>
<tr>
<td>Myocardial Re-infarction</td>
<td>204 (2.0)</td>
<td>379 (3.7)</td>
<td>0.54 (0.45 to 0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>145 (1.4)</td>
<td>247 (2.4)</td>
<td>0.59 (0.48 to 0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or Myocardial Re-infarction or Urgent Revascularization</td>
<td>874 (8.5)</td>
<td>1181 (11.6)</td>
<td>0.74 (0.68 to 0.80)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 26: 100 mg/mL Concentration

<table>
<thead>
<tr>
<th>Dosage Unit/ Strength</th>
<th>Anti-Xa Activity</th>
<th>Package Size (per carton)</th>
<th>Label Color</th>
<th>NDC # 63323-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-Dose Prefilled Syringes2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mg/0.3 mL</td>
<td>3000 IU</td>
<td>10 syringes</td>
<td>Medium Blue</td>
<td>533-83</td>
</tr>
<tr>
<td>40 mg/0.4 mL</td>
<td>4000 IU</td>
<td>10 syringes</td>
<td>Yellow</td>
<td>535-87</td>
</tr>
<tr>
<td>Single-Dose Graduated Prefilled Syringes2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg/0.6 mL</td>
<td>6000 IU</td>
<td>10 syringes</td>
<td>Orange</td>
<td>607-88</td>
</tr>
<tr>
<td>80 mg/0.8 mL</td>
<td>8000 IU</td>
<td>10 syringes</td>
<td>Brown</td>
<td>521-90</td>
</tr>
<tr>
<td>100 mg/1 mL</td>
<td>10,000 IU</td>
<td>10 syringes</td>
<td>Black</td>
<td>605-84</td>
</tr>
<tr>
<td>Multiple-Dose Vial2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg/3 mL</td>
<td>30,000 IU</td>
<td>1 vial</td>
<td>Red</td>
<td>539-03</td>
</tr>
</tbody>
</table>

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

Table 27: 150 mg/mL Concentration

<table>
<thead>
<tr>
<th>Dosage Unit/ Strength</th>
<th>Anti-Xa Activity</th>
<th>Package Size (per carton)</th>
<th>Syringe Label Color</th>
<th>NDC # 63323-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-Dose Graduated Prefilled Syringes2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 mg/0.6 mL</td>
<td>12,000 IU</td>
<td>10 syringes</td>
<td>Purple</td>
<td>609-90</td>
</tr>
</tbody>
</table>

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

The beneficial effect of enoxaparin on the primary endpoint observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2).
Table 27: 150 mg/mL Concentration (continued)

<table>
<thead>
<tr>
<th>Dosage Unit/</th>
<th>Anti-Xa</th>
<th>Package Size</th>
<th>Syringe Label</th>
<th>NDC #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength†</td>
<td>Activity†</td>
<td>(per carton)</td>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>150 mg/1 mL</td>
<td>15,000 IU</td>
<td>10 syringes</td>
<td>Navy Blue</td>
<td>537-84</td>
</tr>
</tbody>
</table>

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

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

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

References

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

†Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
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 prefilled syringe if it has been dropped on a hard surface or damaged.

Figure B

Step 4: Check the enoxaparin sodium prefilled syringe

- When you receive your enoxaparin sodium 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 prefilled syringe if the expiration date has passed.

Figure C

Step 5: Check the medicine

- Look at the medicine inside the enoxaparin sodium prefilled syringe:
  - The liquid should be clear and colorless to pale 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 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.

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

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.

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 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 prefilled syringes and needle caps**
Put the used enoxaparin sodium 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 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**

Manufactured for:
Fresenius Kabi USA, LLC
Lake Zurich, IL 60047

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Issued: December 2021

1 Items not included.

ENOX-F-FPLR-SL-DEC21                  RX Only