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

Recent Major Changes

Inpatient treatment of acute DVT without pulmonary embolism (1.2)

Outpatient treatment of acute DVT without pulmonary embolism (1.2)

Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI) (1.3)

Treatment of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with subsequent percutaneous coronary intervention (PCI) (1.4)

Dosage and Administration

Indication Dose

Acute STEMI in patients <75 years of age 30 mg single intravenous bolus plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg subcutaneously every 12 hours (with aspirin)

Acute STEMI in patients ≥75 years of age 0.75 mg/kg subcutaneously every 12 hours (for bolus) (with aspirin)

• See recommended durations for enoxaparin sodium therapy (2.1)

• See recommendations regarding transitioning to warfarin therapy (2.1)

• Adjust the dose for patients with severe renal impairment (2.2, 8.7)

Dosage Forms and Strengths

100 mg/mL concentration (3.1)

Prefilled syringes: 30 mg/0.3 mL, 40 mg/0.4 mL

Graduated prefilled syringes: 80 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL

Multiple-dose vial: 300 mg/3 mL

150 mg/mL concentration (3.2)

Graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL

CONTRAINDICATIONS

Active major bleeding (4)

History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (4)

Hypersensitivity to enoxaparin sodium (4)

Hypersensitivity to heparin or pork products (4)

Hypersensitivity to benzyl alcohol (for multidose formulation only) (4)

WARNINGS AND PRECAUTIONS

Increased risk of hemorrhage: Use with caution in patients at risk (5.1)

Percutaneous coronary revascularization: Obtain hemostasis at the puncture site before sheath removal (5.2)

Concomitant medical conditions: Use with caution in patients with bleeding diathesis, uncontrolled arterial hypertension or history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction or hemorrhage (5.3)

History of heparin-induced thrombocytopenia: See Contraindications (4). Use may be considered if previous HIT episode was >100 days prior and no circulating antibodies are present (5.4)

Thrombocytopenia: Monitor platelet count closely (5.5)

Interchangeability with other heparins: Do not exchange with heparin or other LMWHs (5.6)

Pregnant women with mechanical prosthetic heart valves, and their fetuses, may be at increased risk and may need more frequent monitoring and dosage adjustment (5.7)

ADVERSE REACTIONS

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum amylotransferase, dizziness, headache, nausea, vomiting, fever, edema, peripheral edema, dyspnea, confusion, 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 (5.9, 7)

Use in Specific Populations

• Severe Renal Impairment: Adjust dose for patients with creatinine clearance <30 mL/min (2.2, 8.7)

• Geriatric Patients: Monitor for increased risk of bleeding (8.5)

• Patients with mechanical heart valves: Not adequately studied (8.6)

• Hepatic Impairment: Use with caution (8.8)

• Low-Weight Patients: Observe for signs of bleeding (8.9)

• Obese Patients: Not adequately studied. Observe for thromboembolism (8.10)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2017

3 Dosage forms and strengths

3.1 100 mg/mL Concentration

3.2 150 mg/mL Concentration

4 Contraindications

5 Warnings and precautions

5.1 Increased Risk of Hemorrhage

5.2 Percutaneous Coronary Revascularization Procedures

5.3 Use of Enoxaparin Sodium with Concomitant Medical Conditions

5.4 History of Heparin-Induced Thrombocytopenia

5.5 Thrombocytopenia

5.6 Interchangeability with Other Heparins

5.7 Pregnant Women with Mechanical Prosthetic Heart Valves

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

5.9 Laboratory Tests

1 Dosage and administration

Indication Dose

DVT prophylaxis in abdominal surgery 40 mg subcutaneously once daily

DVT prophylaxis in knee replacement surgery 30 mg subcutaneously every 12 hours

DVT prophylaxis in hip replacement surgery 30 mg subcutaneously every 12 hours or 40 mg subcutaneously once daily

DVT prophylaxis in medical patients 40 mg subcutaneously once daily

Inpatient treatment of acute DVT with or without pulmonary embolism 1 mg/kg subcutaneously every 12 hours or 1.5 mg/kg subcutaneously once daily

Outpatient treatment of acute DVT without pulmonary embolism 1 mg/kg subcutaneously every 12 hours

Unstable angina and non-Q-wave MI 1 mg/kg subcutaneously every 12 hours

(see recommendations regarding transitioning to warfarin therapy (2.1)

WARNING: SPINAL/EPIDURAL HEMATOMAS

See full prescribing information for complete boxed warning.

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

• Use of indwelling epidural catheters

• Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants

• A history of traumatic or repeated epidural or spinal punctures

• A history of spinal deformity or spinal surgery

• Optimal timing between the administration of 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, 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)

ADVERSE REACTIONS

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum amylotransferase, dizziness, headache, nausea, vomiting, fever, edema, peripheral edema, dyspnea, confusion, 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 (5.9, 7)

USE IN SPECIFIC POPULATIONS

• Severe Renal Impairment: Adjust dose for patients with creatinine clearance <30 mL/min (2.2, 8.7)

• Geriatric Patients: Monitor for increased risk of bleeding (8.5)

• Patients with mechanical heart valves: Not adequately studied (8.6)

• Hepatic Impairment: Use with caution (8.8)

• Low-Weight Patients: Observe for signs of bleeding (8.9)

• Obese Patients: Not adequately studied. Observe for thromboembolism (8.10)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2017

1.1 Prophylaxis of Deep Vein Thrombosis

1.2 Treatment of Acute Deep Vein Thrombosis

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

1.4 Treatment of Acute ST-Segment Elevation Myocardial Infarction

2.1 Adult Dosage

2.2 Renal Impairment

2.3 Geriatric Patients with Acute ST-Segment Elevation Myocardial Infarction

2.4 Administration

Indication Dose

Acute STEMI in patients <75 years of age 30 mg single intravenous bolus plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg subcutaneously every 12 hours (with aspirin)
FULL PRESCRIBING INFORMATION

WARNING: SPINAL/EPIDURAL HEMATOMAS

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

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery
- Optimal timing between the administration of enoxaparin sodium 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 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 thrombolyis and being managed medically or with percutaneous coronary intervention (PCI).

2 DOSAGE AND ADMINISTRATION

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

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

Enoxaparin sodium is not intended for intramuscular administration.

2.1 Adult Dosage

2.1.1 Abdominal Surgery

In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of enoxaparin sodium is 40 mg once a day administered by subcutaneous injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been administered in clinical trials.

2.1.2 Hip or Knee Replacement Surgery

In patients undergoing hip or knee replacement surgery, the recommended dose of enoxaparin sodium is 30 mg every 12 hours administered by subcutaneous injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of 40 mg once a day subcutaneously, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, it is recommended that continued prophylaxis with enoxaparin sodium 40 mg once a day be administered by subcutaneous injection for 3 weeks. The usual duration of administration is 7 to 10 days; up to 14 days administration has been administered in clinical trials.

2.1.3 Medical Patients During Acute Illness

In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of enoxaparin sodium is 40 mg once a day administered by subcutaneous injection. The usual duration of administration is 6 to 11 days; up to 14 days of enoxaparin sodium has been administered in the controlled clinical trial.

Treatment of Deep Ven Thrombosis with or without Pulmonary Embolism

In outpatient treatment, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of enoxaparin sodium is 1 mg/kg every 12 hours administered subcutaneously. In inpatient (hospital) treatment, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of enoxaparin sodium 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. In both outpatient and inpatient (hospital) treatment, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of enoxaparin sodium). Enoxaparin sodium should be continued 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; up to 17 days of enoxaparin sodium administration has been administered in controlled clinical trials.

Treatment of Unstable Angina and Non-Q-Wave Myocardial Infarction

In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of enoxaparin sodium is 1 mg/kg administered subcutaneously every 12 hours in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with enoxaparin sodium should be prescribed for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days; up to 12.5 days of enoxaparin sodium has been administered in clinical trials [see Warnings and Precautions (5.2) and Clinical Studies (14.5)].

Treatment of Acute ST-Segment Elevation Myocardial Infarction

In patients with acute ST-segment elevation myocardial infarction, the recommended dose of enoxaparin sodium 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). Dosage adjustments are recommended in patients ≥75 years of age [see Dosage and Administration (2.2)]. All patients should receive aspirin as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated.

When administered in conjunction with a thrombolytic (tissue plasminogen activator, recombinant), enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy.

In the pivotal clinical study, the enoxaparin sodium treatment duration was 8 days or until hospital discharge, whichever came first. An optimal duration of treatment is not known, but it is likely to be longer than 8 days.

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

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30–50 mL/min) and mild (creatinine clearance 50–80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.

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

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

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

2.3 Geriatric Patients with Acute ST- Segment Elevation Myocardial Infarction

For treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, do not use an initial intravenous bolus. Initiate dosing with 0.75 mg/kg subcutaneously every 12 hours (maximum 75 mg for the first two doses only, followed by 0.75 mg/kg dosing for the remaining doses) [see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]. No dose adjustment is necessary for other indications in geriatric patients unless kidney function is impaired [see Dosage and Administration (2.2)].

2.4 Administration

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.

The use of a tuberculin syringe or equivalent is recommended when using enoxaparin sodium multiple-dose vials to assure withdrawal of the appropriate volume of drug. Enoxaparin sodium must not be administered by intramuscular injection. Enoxaparin sodium is intended for use under the guidance of a physician.

For subcutaneous administration, patients may self-inject only if their physicians determine that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique

Patients should be lying down and enoxaparin sodium administered by deep subcutaneous injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.

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 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.

1. Remove the needle shield by pulling it straight off the syringe (see Figure A). If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient. See Figure A

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

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

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

NOTE:

- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient’s skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.

Activation of the safety system may cause minimal splatter of fluid. For optimal safety, activate the system while orienting it downwards away from yourself and others.

Intravenous (Bolus) Injection Technique

For intravenous injection, the multiple-dose vial should be used. Enoxaparin sodium should be administered through an intravenous line. Enoxaparin sodium should not be mixed or coadministered with other medications. To avoid the possible mixture of enoxaparin sodium with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of enoxaparin sodium or the port of drug. Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

3 DOSAGE FORMS AND STRENGTHS

Enoxaparin sodium injection is available in two concentrations. 3.1 100 mg/mL Concentration

- Prefilled Syringes
  - 30 mg/0.3 mL, 40 mg/0.4 mL
- Graduated Prefilled Syringes
  - 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL
- Multiple-Dose Vials
  - 300 mg/3 mL

3.2 150 mg/mL Concentration

- Graduated Prefilled Syringes
  - 120 mg/0.3 mL, 150 mg/1 mL

4 CONTRAINDICATIONS

- 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)]
- Known hypersensitivity to enoxaparin sodium (e.g., pruritus, urticaria, anaphylactic/anaphylactoid reactions) [see Adverse Reactions (6.2)]
- Known hypersensitivity to heparin or pork products
- Known hypersensitivity to benzyl alcohol (which is in only the multidose formulation of enoxaparin sodium) [see Warnings and Precautions (5.6)]

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 and epidural or spinal anesthesia/analgésia or spinal puncture procedures, resulting in long-term or permanent paraplegia. The risk of these events is higher with the use of postoperative indwelling epidural catheters, with the concomitant use of additional drugs affecting hemostasis such as NSAIDs, with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity [see Boxed Warning, Adverse Reactions (6.2) and Drug Interactions (7)].

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anesthesia/analgésia, 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 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. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial hemostoma 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/min, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of enoxaparin sodium doses. 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), 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 hematoma 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 subcutaneously in a single injection only if certain conditions are met such as increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiolytic gastrointestinal disease, hemarthritic 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. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

5.2 Perioperative Coronary Revascularization Procedures

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, no coronary artery bypass grafting and no percutaneous transluminal coronary angioplasty should be performed until the enoxaparin sodium doses are adjusted precisely to the intervals recommended between enoxaparin sodium 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 dose. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation [see Dosage and Administration (2.1)].

5.3 Use of Enoxaparin Sodium 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 History of Heparin-Induced Thrombocytopenia

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.

In patients with a history of HIT, enoxaparin sodium should only be used 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, 0.2% of patients given enoxaparin sodium, 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 50,000/mm³, enoxaparin sodium should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death [see Warnings and Precautions (5.4)].

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 Pregnant Women with Mechanical Prosthetic Heart Valves

The use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin sodium (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. Spinal/epidural decompression even though such treatment may not prevent or reverse neurological sequelae. Spinal/epidural hematomas [see Warnings and Precautions (5.6)].

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. In 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)].

5.9 Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult/blood tests are recommended during the course of treatment with enoxaparin sodium. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of enoxaparin sodium activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of enoxaparin sodium therapy in patients with significant renal impairment. 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)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

- Pulmonary embolism
- Smoldering thrombosis
- Deep vein thrombosis
- Pulmonary embolism
- Risk of hemorrhage
- Spinal/epidural hematoma

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 1,229 for prophylaxis of deep vein thrombosis following abdominal surgery patients at risk for thromboembolic complications, 1,368 for prophylaxis of deep vein thrombosis following hip or knee replacement surgery, 711 for prophylaxis of deep vein thrombosis in medical patients with severely restricted mobility during acute illness, 1,578 for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, 10,176 for treatment of acute ST-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 of unstable angina and non-Q-wave myocardial infarction doses were 1 mg/kg every 12 hours and in the clinical studies for treatment of acute ST-segment elevation myocardial infarction enoxaparin sodium doses were a 30 mg 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>
<thead>
<tr>
<th>Table 2: Major Bleeding Episodes Following Abdominal and Colorctal Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Regimen</td>
</tr>
<tr>
<td>Abdominal Surgery</td>
</tr>
<tr>
<td>n=555</td>
</tr>
<tr>
<td>Colorectal Surgery</td>
</tr>
<tr>
<td>n=873</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. Retropertitoneal, intracranial, and intracranial hemorrhages were always considered major.

<table>
<thead>
<tr>
<th>Table 3: Major Bleeding Episodes Following Hip or Knee Replacement Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Regimen</td>
</tr>
<tr>
<td>Hip Replacement Surgery with Extended Prophylaxis</td>
</tr>
<tr>
<td>n=288</td>
</tr>
<tr>
<td>Hip Replacement Surgery with Extended Prophylaxis</td>
</tr>
<tr>
<td>n=221</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. Retropertitoneal 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. Injections 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.
Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal or intracranial hemorrhages were always considered major although none were reported during the trial.

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Enoxaparin Sodium</th>
<th>Placebo</th>
<th>Heparin aPTT Adjusted Intravenous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=296</td>
<td>n=559</td>
<td>n=554</td>
<td></td>
</tr>
<tr>
<td>3 (2%)</td>
<td>9 (2%)</td>
<td>9 (2%)</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 by ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intracranial, and intracranial hemorrhages were always considered major.

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Enoxaparin Sodium</th>
<th>Heparin aPTT Adjusted Intravenous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=10176</td>
<td>n=10151</td>
<td></td>
</tr>
<tr>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
</tr>
</tbody>
</table>

Major bleeding (including ICH) up to 30 days

ICH was defined as any intracranial hemorrhage that occurred at a rate of at least 2% in the enoxaparin sodium group, are provided below (see Tables 8 & 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>Placebo</th>
<th>Heparin 5000 U q8h Subcutaneously</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1234</td>
<td>n=1234</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Total</td>
<td>Severe Total</td>
<td>Severe Total</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>&lt;1 6</td>
<td>&lt;1 6</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1 3</td>
<td>&lt;1 3</td>
<td></td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>0 3</td>
<td>0 3</td>
<td></td>
</tr>
</tbody>
</table>

Table 9: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium–Treated Patients Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Enoxaparin Sodium</th>
<th>Placebo</th>
<th>Heparin 15,000 U q8h Subcutaneously</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1115</td>
<td>n=1115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Total</td>
<td>Severe Total</td>
<td>Severe Total</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>&lt;1 2</td>
<td>&lt;1 2</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1 7</td>
<td>&lt;1 7</td>
<td></td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>0 3</td>
<td>0 3</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Adverse Reactions Occurring at ≥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</th>
<th>Placebo</th>
<th>Heparin aPTT Adjusted Intravenous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=360</td>
<td>n=362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Total</td>
<td>Severe Total</td>
<td>Severe Total</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.3</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.6</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>2.2</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>2.2</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2.5</td>
<td>1.7</td>
<td></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 11: Adverse Reactions Occurring at ≥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</th>
<th>Placebo</th>
<th>Heparin aPTT Adjusted Intravenous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=544</td>
<td>n=544</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Total</td>
<td>Severe Total</td>
<td>Severe Total</td>
<td></td>
</tr>
<tr>
<td>Injection Site</td>
<td>0 5</td>
<td>0 3</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>&lt;1 1</td>
<td>&lt;1 1</td>
<td></td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>0 2</td>
<td>0 2</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>0 2</td>
<td>0 2</td>
<td></td>
</tr>
</tbody>
</table>

Data represent enoxaparin sodium 1.5 mg/kg daily subcutaneously or 1 mg/kg q12h subcutaneously.

Data represent enoxaparin sodium 1.5 mg/kg daily subcutaneously or 1 mg/kg q12h subcutaneously.
Adverse Events in Enoxaparin Sodium-Treated Patients with Unstable Angina or Non-Q-Wave Myocardial Infarction

Non-hemorrhagic clinical events reported to be related to enoxaparin sodium therapy occurred at an incidence of <1%. Non-major hemorrhagic events, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with subcutaneous enoxaparin sodium than in patients treated with intravenous heparin.

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

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

| Adverse Event | Enoxaparin Sodium | Dosing Regimen | Heparin
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%): Adjusted Intravenous</td>
<td>n (%):</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (0.70)</td>
<td>3 (0.20)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>15 (0.85)</td>
<td>11 (0.72)</td>
<td></td>
</tr>
<tr>
<td>Lung edema</td>
<td>11 (0.70)</td>
<td>11 (0.72)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13 (0.82)</td>
<td>9 (0.59)</td>
<td></td>
</tr>
</tbody>
</table>

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%.

6.2 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 epidural or spinal anesthesia or spinal puncture. The majority of patients had a postoperative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis.

Local reactions at the injection site (e.g., nodules, inflammation, oozing), systemic allergic reactions (e.g., pruritus, urticaria, anaphylactic/anaphylactoid reactions including shock), vesiculobullous rash, cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thromboembolia 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 to develop the hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparring drugs, administration of potassium, hemotoma in body tissues). Very rare cases of hyperfilleremia have also been reported, with one case of hyperfilleremia, with marked hyperfilleremia, reported in a diabetic pregnant woman; causality has not been determined.

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

Osteoporosis has also been reported following long-term therapy.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes the potential of enoxaparin sodium to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

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

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prothetic 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 by 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 (5.6)].

Data

Tobacco data

There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrage. Major congenital anomalies in live births occurred at rates (2.5%) similar to the general population [see Warnings and Precautions (5.7)].

Animal data

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

8.3 Nursing Mothers

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

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 received drugs containing benzyl alcohol. The maximum tolerated dose of benzyl alcohol in newborns and infants has been reported to be 99–405 mg/kg/day. Benzyl alcohol is not recommended for use in newborns or infants due to the risk of toxicity.

The use of enoxaparin sodium does not increase the risk of major developmental abnormalities. Based on animal 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)].

8.5 Geriatric Use


Over 2800 patients, 65 years or older, have received enoxaparin sodium in pivotal 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. Caution should be exercised in the administration of enoxaparin sodium to geriatric patients. In patients ≥75 years of age, consider decreasing dosage in order to minimize the risk of bleeding.

Use in the elderly is based on clinical studies, post-marketing surveillance and literature reports. 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

When 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 case reports of thrombosis in patients with mechanical prosthetic heart valves have also been reported.

Insufficient clinical trial 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 <15 mL/min) and dialysis patients, enoxaparin has been recommended for therapeutic and dialysis dosage range. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30–50 mL/min) and mild (creatinine clearance 50–80 mL/min) renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]. In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia [see Adverse Reactions (6.2)].

8.8 Hepatic Impairment

The impact of hepatic impairment on enoxaparin’s exposure and antithrombotic effect has not been investigated. Caution should be exercised when administering enoxaparin to patients with hepatic impairment.
8.9 Low-Weight Patients
An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<57 kg) and low-weight men (<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding [see Clinical Pharmacology (12.3)].

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

10 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 sul fate (1% solution). The dose of protamine sul fate should be equal to the dose of enoxaparin sodium injected. 1 mg of protamine sul fate should be administered to neutralize 1 mg of 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 sul fate per 1 mg of enoxaparin sodium may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

If all 12 hours have elapsed since the last enoxaparin sodium injection, protamine administration may not be required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sul fate. Administration of protamine sul fate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sul fate, it should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available. For additional information consult the labeling of protamine sul fate 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 alcoholic deionization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-tuldo-6-enaproyluronic acid group at the non-reducing end and a 2-N,N-diolusulo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain. The drug substance is the sodium salt. The average molecular weight heparin. The pH of the injection is 5.5 to 7.5.

Enoxaparin sodium injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1000 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard)] per 0.1 mL Water for Injection. Enoxaparin sodium injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

Enoxaparin sodium prefilled syringes and graduated prefilled syringes are preservative-free and contain 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.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Enoxaparin sodium 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 versus antithrombin (anti-Factor IIa) activity curves) compared to the ratio observed for heparin (mean ± SD, 1.2 ± 0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose (100 mg/mL concentration), administered subcutaneously every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n=1607). A 30 mg intravenous bolus immediately followed by a 1 mg/kg subcutaneous administration resulted in aPTT postinjection values of 50 seconds. The average aPTT prolongation value on Day 1 was about 16% higher than on Day 4.

12.3 Pharmacokinetics
Absorption
Pharmacokinetic trials were conducted using the 100 mg/mL formulation. Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcutaneous injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 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 given, based on anti-Factor Xa activity is approximately 100% in healthy subjects. A 30 mg intravenous bolus immediately followed by a 1 mg/kg subcutaneously every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 84% of steady-state levels. Steady state is achieved on the second day of treatment.

Enoxaparin pharmacokinetics appears to be linear over the recommended dosage ranges [see Dosage and Administration (2)]. After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once-daily regimens in healthy volunteers, the steady state is reached on day 2 with an average exposure of 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 observed (see Table 13).

<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>150 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±0.08</td>
<td>111±17</td>
<td>22±7</td>
</tr>
<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>90% CI</td>
<td>102%–110%</td>
<td>102%–110%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max T (h)</td>
<td>3 (2–6)</td>
<td>4 (2–5)</td>
<td>2.5 (2–4.5)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>Mean Max (IU/mL or Δ sec)</td>
<td>14.26 (2.93)</td>
<td>1.54 (0.61)</td>
<td>1321 (219)</td>
<td></td>
</tr>
<tr>
<td>AUC (h) (IU/mL or h Δ sec)</td>
<td>15.43 (2.96)</td>
<td>1.77 (0.67)</td>
<td>1401 (227)</td>
<td></td>
</tr>
<tr>
<td>90% CI</td>
<td>105%–110%</td>
<td>105%–110%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Median (range)

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

Exonaparin sodium injection 150 mg/mL Concentration contains 10 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1000 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection. The enoxaparin sodium prefilled syringes and graduated prefilled syringes are preservative-free and intended for single-dose use. The multiple-dose vial contains 15 mg benzyl alcohol per 1 mL as a preservative [see Dosage and Administration (2) and How Supplied (16)].
**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 572 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 43% 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>Dosing Regimen</th>
<th>Placebo</th>
<th>Enoxaparin Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg q12h subcutaneously n (%)</td>
<td>50 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total DVT (%)</td>
<td>67 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>17 (11)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

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

**14.3 Animal Toxicology and/or Pharmacology**

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.

**14.4 Clinical Studies**

**14.4.1 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 1119 patients 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>Dosing Regimen</th>
<th>Heparin vs placebo n (%)</th>
<th>Enoxaparin Sodium vs placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failures Total DVT (%)</td>
<td>63 (11.3)</td>
<td>61 (10.9)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>17 (11)</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

**14.4.2 Prophylaxis of Deep Vein Thrombosis 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 undergoing knee replacement surgery. A total of 132 patients were randomized in the study and 131 patients were treated, of which 99 had total knee replacement and 32 had either unicompartmental knee replacement or tibial osteotomy. The 99 patients with total knee replacement ranged in age from 42 to 85 years (mean age 70.2 years) with 36.4% men and 63.6% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued up to 15 days after surgery. The incidence of proximal and total DVT after surgery was significantly lower for 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>Dosing Regimen</th>
<th>Placebo</th>
<th>Enoxaparin Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg q12h subcutaneously n (%)</td>
<td>50 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total DVT (%)</td>
<td>67 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>17 (11)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

*p value versus placebo = 0.0001
†p value versus placebo = 0.013
‡p value versus placebo = 0.0168
§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 6 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 98.2% 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=82) 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 65.4 years). 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>Enoxaparin Sodium 40 mg daily subcutaneously n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated Extended Prophylaxis Patients</td>
<td>90 (100)</td>
<td>89 (100)</td>
</tr>
<tr>
<td>Treatment Failures Total DVT (%)</td>
<td>6 (7)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>7 (8)</td>
<td>6 (7)</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 56.9% 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 5 [6%] versus placebo 20 [21%]; p<0.001) and proximal VTE.

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 III or IV); acute respiratory failure or complicated chronic respiratory insufficiency (not requiring ventilatory support); acute infection (excluding septic shock); or acute rheumatic disorder (acute lumbar or sciatic pain, vertebral compression [due to osteoporosis or tumor], acute articular episodes of the lower extremities). A total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged in age from 40 to 97 years (mean age 73 years) with equal proportions of men and women. Treatment continued for a maximum of 14 days (median duration 7 days). When given at a dose of 40 mg once a day subcutaneously, 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Enoxaparin Sodium 20 mg daily subcutaneously n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated Medical Patients During Acute Illness</td>
<td>351 (100)</td>
<td>360 (100)</td>
</tr>
<tr>
<td>Treatment Failure Total DVT (%)</td>
<td>43 (12.3)</td>
<td>43 (12.3)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>13 (3.7)</td>
<td>14 (3.7)</td>
</tr>
</tbody>
</table>

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

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, or (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 16 to 92 years (mean age 69.7 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>Enoxaparin Sodium 1.5 mg/kg daily subcutaneously n (%)</th>
<th>Enoxaparin Sodium 1 mg/kg q12h subcutaneously n (%)</th>
<th>Heparin aPTT Adjusted Internavenous Therapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated DVT Patients with or without PE</td>
<td>298 (100)</td>
<td>312 (100)</td>
<td>290 (100)</td>
</tr>
<tr>
<td>Patient Outcome Total VTE* (%)</td>
<td>13 (4.4)</td>
<td>9 (2.8)</td>
<td>12 (4.1)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>9 (3.0)</td>
<td>6 (1.9)</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>PE (%)</td>
<td>2 (0.7)</td>
<td>2 (0.6)</td>
<td>4 (1.4)</td>
</tr>
</tbody>
</table>

*All patients were also treated with warfarin sodium commencing within 72 hours of enoxaparin sodium or standard heparin therapy.
†VTE = venous thromboembolic event (DVT and/or PE)
‡The 95% Confidence Intervals for the treatment differences for total VTE were:
Enoxaparin sodium once a day versus heparin (-3.0 to 3.5)
Enoxaparin sodium every 12 hours versus heparin (-4.2 to 1.7).

Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT were randomized to enoxaparin sodium or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outcome 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 patients were permitted to go home on therapy (72%). A total of 501 patients were randomized in the study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8 years) with 60.5% men and 39.5% women. Patients were randomized to either enoxaparin sodium 1 mg/kg every 12 hours subcutaneously or heparin intravenous bolus (5000 IU) followed by a continuous infusion administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also received warfarin sodium as described in the previous study. Enoxaparin sodium or standard heparin therapy was administered for a minimum of 5 days. Enoxaparin sodium was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are provided below (see Table 22).

### Table 22: Efficacy of Enoxaparin Sodium in Treatment of Deep Vein Thrombosis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Enoxaparin Sodium 1 mg/kg q12h subcutaneously n (%)</th>
<th>Heparin aPTT Adjusted Internavenous Therapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated DVT Patients</td>
<td>247 (100)</td>
<td>254 (100)</td>
</tr>
<tr>
<td>Patient Outcome Total VTE* (%)</td>
<td>13 (5.3)</td>
<td>17 (6.7)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>10 (4.0)</td>
<td>12 (4.7)</td>
</tr>
<tr>
<td>PE (%)</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
</tr>
</tbody>
</table>

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

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

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

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

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

The combined incidence of death or myocardial infarction at all time points was lower for enoxaparin sodium compared to standard heparin therapy, but did not achieve statistical significance. The efficacy data are provided below (see Table 24).

### Table 24: Efficacy of Enoxaparin Sodium in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (Combined endpoint of death or myocardial infarction)

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Enoxaparin Sodium 1 mg/kg q12h subcutaneously n (%)</th>
<th>Heparin aPTT Adjusted Intravenous Therapy n (%)</th>
<th>Reduction (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated Unstable Angina and Non-Q-Wave MI Patients</td>
<td>1578 (100)</td>
<td>1529 (100)</td>
<td>0.1</td>
<td>0.906</td>
</tr>
<tr>
<td>Time point†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 Hours</td>
<td>96 (6.1)</td>
<td>112 (7.3)</td>
<td>1.2</td>
<td>0.120</td>
</tr>
<tr>
<td>14 Days</td>
<td>261 (16.5)</td>
<td>303 (19.8)</td>
<td>3.3</td>
<td>0.017</td>
</tr>
<tr>
<td>30 Days</td>
<td>313 (19.8)</td>
<td>358 (23.4)</td>
<td>3.6</td>
<td>0.014</td>
</tr>
</tbody>
</table>

*All patients were also treated with aspirin 100 to 325 mg per day.
†Evaluation time points are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

In a survey one year following treatment, with information available for 92% of enrolled patients, the combined incidence of death, myocardial infarction, or recurrent angina remained lower for enoxaparin sodium versus heparin (32.9% vs 35.7%).

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

### Table 25: Efficacy of Enoxaparin Sodium in the Treatment of Acute ST-Segment Elevation Myocardial Infarction

<table>
<thead>
<tr>
<th>Outcome at 30 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>478 (4.7)</td>
<td>531 (5.2)</td>
<td>0.90 (0.85 to 1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death</td>
<td>383 (3.7)</td>
<td>390 (3.8)</td>
<td>0.98 (0.85 to 1.12)</td>
<td>0.76</td>
</tr>
<tr>
<td>Myocardial Re-infarction</td>
<td>102 (1.0)</td>
<td>156 (1.5)</td>
<td>0.65 (0.51 to 0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>74 (0.7)</td>
<td>96 (0.9)</td>
<td>0.77 (0.57 to 1.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>Death or Myocardial Re-infarction or Urgent Revascularization</td>
<td>548 (5.3)</td>
<td>622 (6.1)</td>
<td>0.88 (0.79 to 0.97)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*All patients were also treated with aspirin 100 to 325 mg per day.
†Evaluation time points are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

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

Study medication was initiated between 15 minutes before and 30 minutes after the initiation of fibrinolytic therapy. Unfractionated heparin was administered beginning with an intravenous bolus of 60 U/kg (maximum 4000 U) and followed with an infusion of 12 U/kg per hour (initial maximum 1000 U per hour) that was adjusted to maintain an aPTT of 1.5 to 2 times the control value. The intravenous bolus was to be given for at least 48 hours. The enoxaparin dosing strategy was adjusted according to the patient's age and renal function. For patients younger than 75 years of age, enoxaparin was given as a single 30 mg intravenous bolus plus a 1 mg/kg subcutaneous dose followed by a subcutaneous injection of 1 mg/kg every 12 hours. For patients at least 75 years of age, the intravenous bolus was not given and the subcutaneous dose was reduced to 0.75 mg/kg every 12 hours. For patients with severe renal insufficiency (estimated creatinine clearance of less than 30 mL per minute), the dose was to be modulated to 1 mg/kg every 24 hours. The subcutaneous injections of enoxaparin were given until hospital discharge or for a maximum of eight days (whichever came first). The mean treatment duration was 2.6 days.

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

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

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

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*The primary efficacy endpoint was the composite of death from any cause or myocardial re-infarction in the first 30 days. The overall treatment effect of enoxaparin as compared to the unfractionated heparin is shown at the bottom of the figure. For each subgroup, the circle is proportional to the number and represents the point estimate of the treatment effect and the horizontal lines represent the 95% confidence intervals. Fibrin-specific fibrinolytic agents included alteplase, tenecteplase, and reteplase.
The beneficial effect of enoxaparin on the primary endpoint observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2).

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

![Kaplan-Meier Plot](image)

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

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

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

*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.

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

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

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Enoxaparin sodium injection is available in two concentrations (see Tables 26 and 27).

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>Prefilled Syringes¹</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>568-83</td>
</tr>
<tr>
<td>40 mg/0.4 mL</td>
<td>4000 IU</td>
<td>10 syringes</td>
<td>Yellow</td>
<td>568-87</td>
</tr>
<tr>
<td>Graduated Prefilled Syringes¹</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>568-88</td>
</tr>
<tr>
<td>80 mg/0.8 mL</td>
<td>8000 IU</td>
<td>10 syringes</td>
<td>Brown</td>
<td>568-90</td>
</tr>
<tr>
<td>100 mg/1 mL</td>
<td>10,000 IU</td>
<td>10 syringes</td>
<td>Black</td>
<td>568-84</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>565-96</td>
</tr>
</tbody>
</table>

¹Strength 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.
²Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
³Each enoxaparin sodium prefilled syringe is for single, one-time use only and is affixed with a 27 gauge x 1/2 inch needle.
⁴Each enoxaparin sodium multiple-dose vial contains 15 mg benzyl alcohol per 1 mL as a preservative.

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