#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENOXAPARIN SODIUM INJECTION safely and effectively. See full prescribing information for ENOXAPARIN SODIUM INJECTION. ENOXAPARIN SODIUM injection, for subcutaneous and intravenous use

Initial U.S. Approval: 1993

### WARNING: SPINAL/EPIDURAL HEMATOMAS

#### See full prescribing information for complete boxed warning.

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecula ueight heparins (LMWH) or heparinoids and are receiving neuraxil 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 o 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 antiinflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery
- Optimal timing between the administration of enoxaparin sodium injection and neuraxia procedures is not known Monitor patients frequently for signs and symptoms of neurological impairment. If neurological
- compromise is noted, urgent treatment is necessary. (5.1, 7)

## --- INDICATIONS AND USAGE-

- Enoxaparin Sodium Injection is a low molecular weight heparin (LMWH) indicated for: Prophylaxis of deep vein thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness (1.1)
- Inpatient treatment of acute DVT with or without pulmonary embolism (1.2)
- Outpatient treatment of acute DVT without pulmonary embolism (1.2)
- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI)
- $Treatment \ of \ acute \ ST-segment \ elevation \ myocardial \ infarction \ (STEMI) \ managed \ medically \ or \ with \ subsequent \ percutaneous \ coronary \ intervention \ (PCI) \ (1.4)$ -- DOSAGE AND ADMINISTRATIO

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

#### FULL PRESCRIBING INFORMATION: CONTENTS WARNING: SPINAL/EPIDURAL HEMATOMAS

- INDICATIONS AND USAGE 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
- Treatment of Acute ST-Segment Elevation Myocardial Infarction DOSAGE AND ADMINISTRATION
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#### FULL PRESCRIBING INFORMATION

#### WARNING: SPINAL/EPIDURAL HEMATOMAS

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

- · Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-
- inflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery
- Optimal timing between the administration of enoxaparin sodium injection and neuraxia procedures is not known

## Monitor patients frequently for signs and symptoms of neurological impairment. If neurological

## compromise is noted, urgent treatment is necessary.

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

#### INDICATIONS AND USAGE

- 1.1 Prophylaxis of Deep Vein Thrombosis
- Enoxaparin Sodium Injection is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead
- to pulmonary embolism (PE)
  - in patients undergoing abdominal surgery who are at risk for thromboembolic complications [see Clinical Studies (14.1)]
- in patients undergoing hip replacement surgery, during and following hospitalization
- in patients undergoing knee replacement surgery
- · in medical patients who are at risk for thromboembolic complications due to severely restricted
- mobility during acute illness 1.2 Treatment of Acute Deep Vein Thrombosis
- Enoxaparin Sodium Injection is indicated for:
- the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when stered in conjunction with warfarin sodiun
- the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodiun
- Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial 1.3

Enoxaparin Sodium Injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirir

- -DOSAGE FORMS AND STRENGTHS-100 mg per mL concentration (3):
- Single-Dose Prefilled Syringes: 30 mg per 0.3 mL, 40 mg per 0.4 mL
- Single-Dose Graduated Prefilled Syringes: 60 mg per 0.6 mL, 80 mg per 0.8 mL, 100 mg per mL 150 mg per mL concentration (3):
- Single-Dose Graduated Prefilled Syringes: 120 mg per 0.8 mL, 150 mg per mL CONTRAINDICATIONS.
- Active major bleeding (4)
- History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (4)
- Hypersensitivity to enoxaparin sodium (4)
- Hypersensitivity to heparin or pork products (4)
  - -WARNINGS AND PRECAUTIONS-
  - Increased Risk of Hemorrhage: Monitor for signs of bleeding. (5.1, 5.2, 5.3) Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis. (5.4)
  - Thrombocytopenia: Monitor platelet count closely. (5.5)
  - . Interchangeability with other heparins: Do not exchange with heparin or other LMWHs. (5.6)
  - Increased Risk of Thrombosis in Pregnant Women with Mechanical Prosthetic Heart Valves: Women and their fetuses may be at increased risk. Monitor more frequently and adjust dosage as needed. (5.7)

----ADVERSE REACTIONS--

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, nausea, ecchymosis, fever, edema, peripheral edema, dyspnea, confusion, and injection site pain. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Meitheal Pharmaceuticals Inc. at 1-844-824-

#### 8426 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. -----DRUG INTERACTIONS

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

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

See 17 for PATIENT COUNSELING INFORMATION

#### Revised: 07/2019

Pediatric Use

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

Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility

Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardia

(no initial bolus)

Thromboembolic Complications Prophylaxis of Deep Vein Thrombosis following Hip or Knee Replacement Surgery

Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

Treatment of acute ST-segment elevation myocardial 1 mg/kg administered subcutaneously once daily

Although no dose adjustment is recommended in patients with creatinine clearance 30 to 50 mL/min and

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)

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

Enoxaparin sodium injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral

Patients may self-inject by the subcutaneous route of administration only after their physicians determine that

it is appropriate and with medical follow-up, as necessary. Provide proper training in subcutaneous injection technique before allowing self-injection (with or without the assistance of an injection device).

· Position patients in a supine position for enoxaparin sodium injection administration by deep

· Do not expel the air bubble from the prefilled syringes before the injection, to avoid the loss of drug.

· Alternate injection sites between the left and right anterolateral and left and right posterolateral

Introduce the whole length of the needle into a skin fold held between the thumb and forefinger.

Enoxaparin sodium injection prefilled syringes and graduated prefilled syringes are for single, one-time use

Remove the prefilled syringe from the blister packaging by peeling at the arrow as directed on the blister. Do

hold the skin fold throughout the injection. To minimize bruising, do not rub the injection site after

Remove the needle shield by pulling it straight off the syringe (see Figure A). If less than the

full syringe volume is needed to administer the prescribed dose, eject syringe contents until the

drug products, should be inspected visually for particulate matter and discoloration prior to administration

creatinine clearance 50 to 80 mL/min, observe these patients frequently for signs and symptoms of bleeding.

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

Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

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Animal Toxicology and/or Pharmacology Reproductive and Developmental Toxicology

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Pregnancy

Lactation

8.9 Obese Patients

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- OVERDOSAGE
- DESCRIPTION 12 CLINICAL PHARMACOLOGY
- Mechanism of Action

CLINICAL STUDIES

12.2 Pharmacodynamics 12.3 Pharmacokinetics NONCLINICAL TOXICOLOGY

during Acute Illness

HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

infarction in geriatric patients ≥75 years of age, when

[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]

Do not administer enoxaparin sodium injection by intramuscular injection

only and are available with a system that shields the needle after injectior

not remove by pulling on the plunger as this may damage the syringe

Administer enoxaparin sodium injection by intravenous or subcutaneous injection only.

Infarction

administered in conjunction with aspirin

2.5 Administration

Subcutaneous Injection Technique

abdominal wall.

subcutaneous injectio

completion of the injection.

prescribed dose is left in the syringe.

#### 1.4 Treatment of Acute ST-Segment Elevation Myocardial Infarction

Enoxaparin Sodium Injection, when administered concurrently with aspirin, has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction (STEMI) receiving thrombolysis and being managed medically or with percutaneous coronary intervention (PCI)

#### DOSAGE AND ADMINISTRATION 2

#### 2.1 Pretreatment Evaluation

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

#### 2.2 Adult Dosage

#### Abdominal Surgery

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

#### Hip or Knee Replacement Surgery

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

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

#### Medical Patients During Acute Illness

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

#### Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

The recommended dose of enoxaparin sodium injection is 1 mg/kg every 12 hours administered subcutaneously in patients with acute deep vein thrombosis without pu at home in an outpatient setting.

The recommended dose of enoxaparin sodium injection is 1 mg/kg every 12 hours administered subcutaneously or 1.5 mg/kg once a day administered subcutaneously at the same time every day for inpatient (hospital) treatment of patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatien) treatment).

In both outpatient and inpatient (hospital) treatments, initiate warfarin sodium therapy when appropriate In both oblaction and influence in a property of the second second second second and the second seco 2 to 3). The average duration of administration is 7 days [see Clinical Studies (14.4)].

#### Unstable Angina and Non-Q-Wave Myocardial Infarction

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

#### Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

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

For patients managed with percutaneous coronary intervention (PCI), if the last enoxaparin sodium injection The patients managed with percentions are interested as the participation of the patients of the patients of the patient of th before balloon inflation, administer an intravenous bolus of 0.3 mg/kg of enoxaparin sodium injection [see Warnings and Precautions (5.2)1.

#### 2.3 Dose Reduction for Patients with Severe Renal Impairment

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

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

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



Figure A

Figure C

Figure D

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



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



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).



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



- · 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

NOTE

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

#### 2.6 Monitoring for Safety

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

#### Assess for signs and symptoms of bleeding.

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

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

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

#### 3 DOSAGE FORMS AND STRENGTHS

Enoxaparin Sodium Injection, USP is available in two concentrations

### 100 mg per mL Concentration

- Single-Dose Prefilled Syringes
- Single-Dose Graduated Prefilled Svringes 60 mg per 0.6 mL, 80 mg per 0.8 mL, 100 mg per mL

30 mg per 0.3 mL, 40 mg per 0.4 mL

- 150 mg per mL Concentration
  - Single-Dose Graduated Prefilled Syringes 120 mg per 0.8 mL, 150 mg per mL

#### CONTRAINDICATIONS 4

Enoxaparin sodium is contraindicated in patients with:

- Active major bleeding
- History of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies [see Warnings and Precautions (5.4)]

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)

Known hypersensitivity to enoxaparin sodium (e.g., pruritus, urticaria, anaphylactic/anaphylactoid

Cases of epidural or spinal hemorrhage and subsequent hematomas have been reported with the use of enoxaparin sodium injection and epidural or spinal anesthesia/analgesia or spinal puncture procedures, resulting in long-term or permanent paralysis. The risk of these events is higher with the use of postoperative

indwelling epidural catheters, with the concomitant use of additional drugs affecting hemostasis such as

NSAIDs, with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity [see Boxed Warning, Adverse Reactions (6.2) and Drug Interactions (7)].

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural

or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin [see Clinical Pharmacology (12.3)]. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticcagulant effect of enoxaparin is low; however, the exact timing to reach a sufficiently

Placement or removal of a catheter should be delayed for at least 12 hours after administration of lower doses

(30 mg once or twice daily or 40 mg once daily) of enoxaparin sodium injection, and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of

enoxaparin sodium injection. Anti-Xa levels are still detectable at these time points, and these delays are not a

guarantee that neuraxial hematoma will be avoided. Patients receiving the 0.75 mg/kg twice-daily dose or the 1 mg/kg twice-daily dose should not receive the second enoxaparin dose in the twice-daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing

of a subsequent enoxaparin sodium dose after catheter removal cannot be made, consider delaying this pert dose for at least four hours based on a benefit-risk assessment considering both the risk for through

and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine

clearance <30 mL/minute, additional considerations are necessary because elimination of enoxaparin is more

prolonged: consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed

dose of enoxaparin sodium (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day) [see

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

Insurgional impairment such as midline back pain, sensory and motor deficits (numberss or weakness in lower limbs), and bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience

any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent

Use enoxaparin sodium injection with extreme caution in conditions with increased risk of hemorrhage, such

as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic

pastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these

Bleeding can occur at any site during therapy with enoxaparin sodium injection. An unexplained fall in

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina,

non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to

the intervals recommended between encovaparin sodium injection doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately

If a manual compression method is used, sheath should be removed 6 hours after the last intravenous

subcutaneous enoxaparin sodium injection. If the treatment with enoxaparin sodium is to be continued

the next scheduled dose should be given no sconer 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]

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

Enoxaparin sodium may cause Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced

Use of enoxaparin sodium in patients with a history of immune-mediated HIT within the past 100 days or in the

Only use enoxaparin sodium in patients with a history of HIT if more than 100 days have elapsed since

the prior HIT episode and no circulating antibodies are present. Because HIT may still occur in these circumstances, the decision to use enoxaparin sodium in such a case must be made only after a careful benefit-risk assessment and after non-heparin alternative treatments are considered.

Moderate thrombocytopenia (platelet counts between 100.000/mm<sup>3</sup> and 50.000/mm<sup>3</sup>) occurred at a rate of

Platelet counts less than 50,000/mm<sup>3</sup> occurred at a rate of 0.1% in patients given enoxaparin sodium, in 0.2%

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm<sup>3</sup> enoxaparin sodium should be discontinued.

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.

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

Use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves

given enoxaparin (1 mg/kg twice daily) to reduce the risk of thrombombolism, 2 of 8 women developed clots

resulting in blockage of the valve and leading to maternal and fetal death. No patients in the heparin/warfarir

group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy

and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion, and premature

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

During clinical development for the approved indications, 15,918 patients were exposed to enorabarin sodium

These included 1,228 for prophylaxis of deep vein thrombosis following abdominal surgery in patients at risk for thromboembolic complications, 1,368 for prophylaxis of deep vein thrombosis following hip or knee

replacement surgery, 711 for prophylaxis of deep vein thrombosis in medical patients with severely restricted

wobility 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 surger

of unstable angina and non-Q-wave myocardial infarction doses were 1 mg/kg every 12 hours and in the

or in medical patients with severely restricted mobility during acute illness ranged from 40 mg subcutaneous once daily to 30 mg subcutaneously twice daily. In the clinical studies for prophylaxis of ischemic complication

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

• Increased Risk of Hemorrhage [see Warnings and Precautions (5.1)]

Thrombocytopenia [see Warnings and Precautions (5.5)]

• Spinal/epidural hematomas [see Boxed Warning and Warnings and Precautions (5.1)]

nitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may

1.3% in patients given enoxaparin sodium, 1.2% in patients given heparin, and 0.7% in patients given pl

mbocytopenia with Thrombosis (HITTS). HITTS may lead to organ infarction, limb ischemia, or death

Increased Risk of Bleeding in Patients with Concomitant Medical Conditions

Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis

presence of circulating antibodies is contraindicated [see Contraindications (4)]

Thrombocytopenia can occur with the administration of enoxaparin sodium.

of patients given heparin, and 0.4% of patients given placebo in the same trials

Interchangeability with other Heparins

Increased Risk of Bleeding following Percutaneous Coronary Revascularization Procedures

diagnosis and treatment including consideration for spinal cord decompression even though such trea

reactions) [see Adverse Reactions (6.2)]

WARNINGS AND PRECAUTIONS

low anticoagulant effect in each patient is not known.

Clinical Pharmacology (12.3)].

cases have been fatal

5.2

(2.1)].

hemorrhage

5.3

5.4

may not prevent or reverse neurological seguelae

patients treated concomitantly with platelet inhibitors.

Monitor thrombocytopenia of any degree closely.

Circulating antibodies may persist for several years

5.5 Thrombocytopenia

delivery. Therefore, frequent mo

be needed [see Use in Specific Populations (8.6)].

ADVERSE REACTIONS

6.1 Clinical Trials Experience

reflect the rates observed in clinical practice.

in clinical trials

5.6

5.7

hematocrit or blood pressure should lead to a search for a bleeding site

Increased Risk of Hemorrhage

5

5.1

· Known hypersensitivity to heparin or pork products

#### Table 2: Major Bleeding Episodes Following Abdominal and Colorectal Surgery'

for treatment of acute ST-segment elevation myocardial in

	Dos	ing Regimen
	Enoxaparin Sodium	Heparin
Indications	40 mg daily subcutaneously	5,000 U q8h subcutaneously
Abdominal Surgery	n=555	n=560
	23 (4%)	16 (3%)
Colorectal Surgery	n=673	n=674
	28 (4%)	21 (3%)

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

#### Table 3: Major Bleeding Episodes Following Hip or Knee Replacement Surgery

	D	osing Regimen	
Indications	Enoxaparin Sodium 40 mg daily subcutaneously	Enoxaparin Sodium 30 mg q12h subcutaneously	Heparin 15,000 U/24h subcutaneously
Hip Replacement Surgery without Extended Prophylaxis <sup>†</sup>		n=786 31 (4%)	n=541 32 (6%)
Hip Replacement Surgery with Extended Prophylaxis			
Peri-operative Period <sup>‡</sup>	n=288 4 (2%)		
Extended Prophylaxis Period <sup>§</sup>	n=221 0 (0%)		
Knee Replacement Surgery without Extended Prophylaxis <sup>†</sup>		n=294 3 (1%)	n=225 3 (1%)

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

<sup>§</sup> Enoxaparin sodium 40 mg subcutaneously once a day for up to 21 days after discharge

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

#### Table 4: Major Bleeding Episodes in Medical Patients with Severely Restricted Mobility During Acute Illness\*

	Dosing Regimen		
	Enoxaparin Sodium <sup>†</sup>	Placebo <sup>†</sup>	
Indication	20 mg daily subcutaneously	40 mg daily subcutaneously	
Medical Patients During	n=351	n=360	n=362
Acute Illness	1 (<1%)	3 (<1%)	2 (<1%)

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

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

<sup>1</sup> Bleeding complications were considered major; (1) if the hemorrhage caused a significant clinical event, or All patients also received warfarin sodium (dose-adjusted according to TP to achieve an INR of 2.0 to 3.0)

encing within 72 hours of enoxaparin sodium or standard heparin therapy and continuing for up to 90 days

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

	Dosing Regimen		
Indication	Enoxaparin Sodium* 1 mg/kg q12h subcutaneously	Heparin* aPTT Adjusted Intravenous Therapy	
Unstable Angina and Non-Q- Wave MI <sup>1.‡</sup>	n=1578 17 (1%)	n=1529 18 (1%)	

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

Aspirint therapy was administered concurrently (100 to 325 mg perday). Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Athar Indillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0 59)

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

Indication

Acute ST-Segment Elevation

yocardial Infarction Major bleeding (including ICH)<sup>1</sup>

Intracranial hemorrhages (ICH)

Elevations of Serum Aminotransferases

interpreted with cautior

Adverse Reaction

lemorrhage

Anemia

Adverse

Reactior

lemorrhage

ever

Nausea

nemia

Peripheral

one clinical trial

Adverse Reaction

rombocytopenia

dverse Reactio

njection Site

emorrhage

Hematuria

Infarction

of ≤1%

. heparin

Adverse Event

provided below (see Table 12).

Injection Site Pain

Undergoing Treatment of Deep Vein Throm

Dyspnea

Confusion

arrhea

Nausea

up to 21 days in one clinical tria

Edema

edema

Ecchymosis

Local Reactions

sodium.

Enoxaparin Sodium'

Initial 30 mg intravenous bolus

followed by

1 mg/kg q12h subcutaneousl

n=10176

n (%) 211 (2.1)

84 (0.8)

The rates represent major bleeding (including ICH) up to 30 days Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by ≥5 g/dL. ICH were always considered major.

Asymptomatic increases in aspartate (AST (SGOTI) and alanine (ALT (SGPTI) aminotransferase levels greater

Asymptoticate indicates in applicate (ACF) EOCT (and Balance (ACF) EOCT (a) minimum and reade to read greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with enoxaparin sodium.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver

disease, and pulmonary emboli, elevations that might be caused by drugs like enoxaparin sodium should be

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

Other adverse reactions that were thought to be possibly or probably related to treatment with enoxaparin

sodium, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery.

abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the

Table 8: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Patients

Enoxaparin Sodium

n=1228

%

Table 9: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Patients

Tota

**Dosing Regime** 

ously

Total

5

4

3

2

2

Enoxaparin Sodium

30 mg q12h

n=1080

subcuta

Severe

<1

<1

<1

<1

<1

<1

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

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

Table 10: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Medical

**Enoxaparin Sodium** 

n=360

3.3

2.8

2.2

2.5

Table 11: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Patients

40 mg daily subcutar

40 mg daily subcuta

Severe

<1

<1

Dosing Regimen

Severe

<1

<1

Heparin 15,000 U/24h

n=766

Severe Total

4

4

2

5

2

4

**Placebo** 

daily subcutaneously

n=362

5.2

2.8

1.1

Heparin aPTT Adjusted

Intravenous Thera

n=544

Tota

Severe

<1

0

<1

Heparin aPTT Adjusted

Intravenous Therapy

n=1529

n (%)

<1

1

<1

2

<1

<1

Dosing Regimen

osis with or without Pulmonary Embolism

Dosing Regimen

Enoxaparin Sodium

1 mg/kg q12h

n=559

Tota

Dosing Regimer

subcu

Severe

Adverse Events in Enoxaparin Sodium-Treated Patients with Unstable Angina or Non-Q-Wave Myocardial

Non-hemorrhagic clinical events reported to be related to enoxaparin sodium therapy occurred at an incidence

Non-major hemorrhagic events, primarily injection site ecchymosis and hematomas, were more frequently

reported in patients treated with subcutaneous enoxaparin sodium than in patients treated with intravenous

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

Table 12: Serious Adverse Events Occurring at ≥0.5% Incidence in Enoxaparin Sodium-Treated

Enoxaparin Sodium

1 mg/kg q12h subcutaneously

n=1578

n (%)

Adverse Reactions in Patients Receiving Enoxaparin Sodium for Prophylaxis or Treatment of DVT, PE

enoxaparin sodium group, are provided below (see Tables 8 to 11).

Undergoing Abdominal or Colorectal Surgery

Undergoing Hip or Knee Replacement Surgery

Peri-operative

Period

n=288

0

<1 13 0 5

Enoxaparin Sodium

40 mg daily

subcutaneously

Severe Total Severe Total

16

8 0 0

Patients with Severely Restricted Mobility During Acute Illness

Enoxaparin Sodium

1.5 mg/kg daily

n=298

Total

Severe

Patients with Unstable Angina or Non-Q-Wave Myocardial Infarction

Extended

Prophylaxi

Period

n=131

<2

Dosing Regime

Heparin\*

aPTT Adjusted

Intravenous Therapy

n=10151

n (%) 138 (1.4)

66 (0.7

<u>Heparin</u>

5,000 U g8h subcutaneously

n=1234

%

Total

6

Placebo

a12h

n=115

Severe Tota

0 3

0 2

3

2

0

<1

0

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 epidural or spinal hematoma formation with concurrent use of enoxaparin sodium and spinal/epidural anesthesia or spinal puncture. The majority of patients had a postoperative indw 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

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 n the injection site), thrombocytosis, and thrombocytopenia with thrombosis [see Warnings and Precautions (5.5)] have been reported.

Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues). Very rare cases of hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

Cases of headache, hemorrhagic anemia, eosinophilia, alopecia, hepatocellular and cholestatic liver injury ve been reporter

Osteoporosis has also been reported following long-term therapy.

#### DRUG INTERACTIONS

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

Placental transfer of enoxaparin was observed in the animal studies. Human data from a retrospective

cohort study, which included 693 live births, suggest that enoxaparin does not increase the risk of major developmental abnormalities (see Data). Based on animal data, enoxaparin is not predicted to increase the risk of major developmental abnormalities (see Data).

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The

estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with Hornbornbolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see Warnings and

Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and

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

It is not known if monitoring of anti-Factor Xa activity and dose adjustment (by weight or anti-Factor Xa activity) of enoxaparin sodium affect the safety and the efficacy of the drug during pregnancy.

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

There have been postmarketing reports of fetal death when pregnant women received enoxaparin sodium.

Causality for these cases has not been determined. Insufficient data, the underlying disease, and the

A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been

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). 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

possibility of inadequate anticoagulation complicate the evaluation of these cases.

hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

with inherited or acquired thrombophilias, have an increased risk of other maternal complications

#### USE IN SPECIFIC POPULATIONS

Precautions (5.7) and Use in Specific Populations (8.6)].

etal loss regardless of the type of anticoagulant used.

conducted [see Warnings and Precautions (5.7)].

8 8.1 Pregnancy

7

### Risk Summary

**Clinical Considerations** 

administered during pregnancy.

Data

Human Data

Animal Data

only if clearly needed.

#### Risk Summary

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

#### 8.4 Pediatric Use

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

#### 8.5 Geriatric Use

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

Over 2800 patients, 65 years and older, have received enoxaparin sodium in clinical trials. The efficacy of enoxaparin sodium in the geriatric (<a>f</a> (see a similar to that seen in younger patients (<a>f</a> (see a similar to that seen in younger patients (<a>f</a> (see a 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 of 1 mg/kg every 12 hours. The risk of encoraparin sodium-associated bleeding increased with age. Serious adverse events increased with age for patients receiving encoraparin sodium. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin sodium between geriatric and suports has not reader additional uniformed in the addy of the additional between the additional provides and a younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Enoxaparin sodium should be used with care in geriatric patients who may show delayed elimination of enoxaparin. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered [see Warnings and Precautions (2.6) and Clinical Pha rmacology (12.3)]

#### Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

#### 8.6 Patients with Mechanical Prosthetic Heart Valves

The use of enoxaparin sodium 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 population, solution and the second encoder of the second encoder in the second population solution and the second encoder in the se underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism [see Warnings and Precautions (5.7)].

#### 8.7 Renal Impairment

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

#### 8.8 Low-Weight Patients

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). Observe low-weight patients frequently for signs and symptoms of bleeding [see Clinical Pharmacology (12.3)].

#### 8.9 Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses To be particular to a higher has for monocommons, the same and the model of polynamic data of encomparison sodium in obsept patients (BMI) 30 (sq/m<sup>2</sup>) has not been fully determined and there is no consensus for dose adjustment. Observe these patients carefully for signs and symptoms of thromboembolism

#### 10 OVERDOSAGE

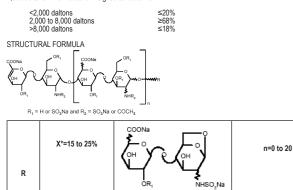
Accidental overdosage following administration of enoxaparin sodium may lead to hemorrhagic complications. Injected encomparin sodium may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of encomparin sodium injected 1 mg protamine sulfate should be administered to neutralize 1 mg encomparin sodium, if encomparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of encomparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administered in enotaparini source in a source and a source of the protamine administered greater than a hours previous of the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of enoxaparin sodium may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

If at least 12 hours have elapsed since the last enoxanarin sodium injection, protamine administration may n at each a not a required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

#### DESCRIPTION

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

Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine Introducing and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains a 1.6 anhydro derivative on the reducing end of the polysaccharide chain. The drug substance is the sodium salt. The average molecular weight is about 4,500 daltons. The molecular weight distribution is:



100-X n=1 to 21 \* X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end Enoxaparin Sodium Injection, USP 100 mg per mL Concentration contains 10 mg er

(approximate anti-Factor Xa activity of 1,000 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection. Enoxaparin Sodium Injection, USP 150 mg per mL Concentration contains 15 mg enoxaparin sodium

Dosage and Administration (2.4) and Use in Specific Populations (8.5)]. Renal Impairment

A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady state has been observed, which indicates decrease clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady state, is marginally increased in patients with creatinine clearance 50 to 80 mL/min and patients with creatinine clearance 30 to <50 mL/min renal impairment after repeated subcutaneous 40 mg once-daily doses. In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC at steady state is significantly increased on average by 65% after repeated subcutaneous 40 mg once-daily doses [see Dosage and Administration (2.3) and Use in Specific Descriptions (2.3) and Use in Specific Descrip Populations (8,7)1.

#### Hemodialvsis

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

#### Hepatic Impairment

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

After repeated subcutaneous 1.5 mg/kg once-daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30 to 48 kg/m<sup>2</sup>) compared to non-obese control subjects, while Amax is not increased.

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

No pharmacokinetic interaction was observed between enoxaparin and thrombolvtics when administered

#### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in in vitro tests, including the Ames test, mouse lymphoma cell forward Encode and was not induspend in *in vitro* tests, including the Ames test, mouse influence of notward was not induspend to the invitro rest. And the invitro rest bare marrow chromosomal aberration test. Encode and was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m<sup>2</sup>)

#### 13.2 Animal Toxicology and/or Pharmacology

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

#### 13.3 Reproductive and Developmental Toxicology

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

#### CLINICAL STUDIES

#### Prophylaxis of Deep Vein Thrombosis following Abdominal Surgery in Patients at Risk for 14.1 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, wordsgrad, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Asian and 0.4% others. Enoxaparin sodium 40 mg subcutaneously, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5,000 U every 8 hours subcutaneously in reducing the risk of DVT. The efficacy data are provided below (see Table 14).

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

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

CI = Confidence Interval

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

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

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

<sup>†</sup> CI = Confidence Interval 14.2 Prophylaxis of Deep Vein Thrombosis following Hip or Knee Replacement Surgery

ndicat

All Trea

reatm

Total

Prox

n value versus placebo

Replacement Surgery

All Treated Hip Replacement

dication

atients reatment Failure

Total DVT (%)

Proximal DVT (%)

Knee Replacement Surgery

eatment Failure

Total DVT (%)

Proximal DVT (%)

p value versus placebo = 0.0001

p value versus enoxaparin sodium 10 mg once a day = 0.000

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

p value versus placebo = 0.0134

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 a doubte with hip replacement. A total of 100 patients were randomized in the study and all patients were treated. Patients ranged in age from 41 to 84 years (mean age 67.1 years) with 45% men and 55% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued for 10 to 14 days after surgery. The efficacy data are provided below (see Table 16).

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

ement Surgery	ent Surgery				
	Dosing Regimen				
	Enoxaparin Sodium Placebo				
	30 mg q12h	q12h			
ion	subcutaneously n (%)	subcutaneously n (%)			
ted Hip Replacement Patients	50 (100)	50 (100)			
ent Failures I DVT (%)	5 (10)*	23 (46)			
imal DVT (%)	1 (2) <sup>†</sup>	11 (22)			

A double-blind, multicenter study compared three dosing regimens of enoxaparin sodium in patients with hip

replacement. A total of 572 patients were randomized in the study and 568 patients were treated. Patients

ranged in age from 31 to 88 years (mean age 64.7 years) with 63% mean and 37% women. Patients were 93% Caucasian, 6% Black, <1% Asian, and 1% others. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The efficacy data are provided below (see Table 17).

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

10 mg daily

subcutaneously

n (%)

161 (100)

40 (25)

17 (11)

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens. In a double-blind study, enoxaparin sodium 30 mg every 12 hours subcutaneously was compared to placebo in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the study and

treatment was initiated 12 to 24 hours after surgery and was continued up to 15 days after surgery. The

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

Enoxaparin Sodium

30 mg q12h

subcutaneously

n (%)

47 (100)

5 (11)\* (95% CI<sup>†</sup>: 1 to 21)

0 (0)

(95% Upper CL§: 5)

131 patients were treated, of which 99 had total knee replacement and 32 had either unicompartme the platents were readed, of which is had total whee replacement and 32 had enter unique from 42 how whee replacement or tibil of sectormy. The 9p platients with total knee replacement or tibil of sectormy. The 9p platients with total knee replacement and as a sector as

incidence of proximal and total DVT after surgery was significantly lower for enoxaparin sodium comp placebo. The efficacy data are provided below (see Table 18).

Dosing Regimen

30 mg q12h

subcutaneously

n (%)

208 (100)

22 (11)\*

8 (4)

Dosing Regime

40 mg daily

subcutaneously

n (%)

199 (100)

27 (14)

9 (5)

Placebo

q12h

subcutaneously

n (%)

52 (100)

32 (62) (95% CI: 47 to 76)

7 (13)

(95% CI: 3 to 24)

red to

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%]) userus placebo, a 51.2% [U approx placebo, 45.12% [U approx versus placebo 45 [34%]; p=0.001) and proximal DVT (enoxaparin sodium 8 [6%] versus placebo 28 [21 p=<0.001).

14.3 Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility during Acute Illnes

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 osis or tumor], acute arthritic episodes of the lower extremities). A total of 1102 patients were enrolled osteoporosis or fumor, acute attrinuc episodes or the lower externities). A total of 1102 patients where ennihee 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

	Dosing Regimen			
	Enoxaparin Sodium 20 mg daily subcutaneously	Enoxaparin Sodium 40 mg daily subcutaneously	<u>Placebo</u>	
Indication	n (%)	n (%)	n (%)	
All Treated Medical Patients During Acute Illness				
	351 (100)	360 (100)	362 (100)	
Treatment Failure* Total VTE <sup>†</sup> (%)	43 (12.3)	16 (4.4)	43 (11.9)	
Total DVT (%)	43 (12.3) (95% Cl <sup>‡</sup> 8.8 to 15.7)	16 (4.4) (95% Cl <sup>‡</sup> 2.3 to 6.6)	41 (11.3) (95% Cl <sup>‡</sup> 8.1 to 14.6)	
Proximal DVT (%)	13 (3.7)	5 (1.4)	14 (3.9)	

Treatment failures during therapy, between Days 1 and 14 VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic

### <sup>‡</sup> CI = Confidence Interva

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

#### 14.4 Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

In a multicenter, parallel group study, 900 patients with acute lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) enoxaparin sodium 1.5 mg/kg once a day subcutaneously, (ii) enoxaparin sodium 1 mg/kg every 12 hours subcutaneously, or (iii) heparin intravenous bolus (5,000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 60.7 years) with 54.7% men and 45.3% women. All patients also received warfarin sodium (dose adjusted according to PT to achieve an International Normalization Ratio [INR] of 2.0 to 3.0), commencing within 72 hours of initiation of enoxaparin sodium or standard heparin therapy, and continuing for 90 days. Enoxaparin sodium or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both enoxaparin sodium regimens were equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism (DVT and/or PE). The efficacy data are provided below (see Table 21).

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

		Dosing Regimen*		
	Enoxaparin Sodium 1.5 mg/kg daily subcutaneously	Enoxaparin Sodium 1 mg/kg q12h subcutaneously	Heparin aPTT Adjusted Intravenous Therapy	
Indication	n (%)	n (%)	n (%)	
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)	
Patient Outcome Total VTE <sup>†</sup> (%)	13 (4.4) <sup>‡</sup>	9 (2.9) <sup>‡</sup>	12 (4.1)	
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)	
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)	
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)	

\* 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 Similarly, in a malucenter, opernease, paraller group study, patents with acute proximatory in we randomized to enoxaparin sodium or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outpatient exclusion criteria included the following: inability to receive outpatient heparin therapy because of associated comorbid conditions or potential for non-compliance and inability to attend follow-up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but ONLY enoxaparin sodium 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 (5,000 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 arin ther 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 Thrombosi

	Dosing	Regimen*
	Enoxaparin Sodium 1 mg/kg q12h subcutaneously	Heparin aPTT Adjusted Intravenous Therapy
Indication	n (%)	n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome Total VTE <sup>†</sup> (%)	13 (5.3) <sup>‡</sup>	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	3 (1.2)

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 (PEI) 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

In a multicenter, double-blind, parallel group study, patients who recently experienced unstable angina or and matching of the second starts of the second sta 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 Table 25: Efficacy of Enoxaparin Sodium in the Treatment of Acute ST-Segment Elevation Myocardial

Indiction				
	Enoxaparin (N=10,256)	UFH (N=10,223)	Relative Risk (95% CI)	P Value
Outcome at 48 hours	n (%)	n (%)		
Death or Myocardial Re-infarction	478 (4.7)	531 (5.2)	0.90 (0.80 to 1.01)	0.08
Death	383 (3.7)	390 (3.8)	0.98 (0.85 to 1.12)	0.76
Myocardial Re-infarction	102 (1.0)	156 (1.5)	0.65 (0.51 to 0.84)	<0.001
Urgent Revascularization	74 (0.7)	96 (0.9)	0.77 (0.57 to 1.04)	0.09
Death or Myocardial Re-infarction or				
Urgent Revascularization	548 (5.3)	622 (6.1)	0.88 (0.79 to 0.98)	0.02
Outcome at 8 Days				
Death or Myocardial Re-infarction	740 (7.2)	954 (9.3)	0.77 (0.71 to 0.85)	< 0.001
Death	559 (5.5)	605 (5.9)	0.92 (0.82 to 1.03)	0.15
Myocardial Re-infarction	204 (2.0)	379 (3.7)	0.54 (0.45 to 0.63)	<0.001
Urgent Revascularization	145 (1.4)	247 (2.4)	0.59 (0.48 to 0.72)	<0.001
Death or Myocardial Re-infarction or				
Urgent Revascularization	874 (8.5)	1181 (11.6)	0.74 (0.68 to 0.80)	<0.001
Outcome at 30 Days				
Primary efficacy endpoint				
(Death or Myocardial Re-infarction)	1017 (9.9)	1223 (12.0)	0.83 (0.77 to 0.90)	0.000003
Death	708 (6.9)	765 (7.5)	0.92 (0.84 to 1.02)	0.11
Myocardial Re-infarction	352 (3.4)	508 (5.0)	0.69 (0.60 to 0.79)	<0.001
Urgent Revascularization Death or Myocardial Re-infarction or	213 (2.1)	286 (2.8)	0.74 (0.62 to 0.88)	<0.001
Urgent Revascularization	1199 (11.7)	1479 (14.5)	0.81 (0.75 to 0.87)	<0.001
lote: Urgent revascularization denotes e	pisodes of recurr	ent mvocardial is	chemia (without infarction	n) leading

the clinical decision to perform coronary revascularization during the same hospitalization. CI denotes confidence

The beneficial effect of enoxaparin on the primary endpoint was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, fibrinolytic agent inistered, and time to treatment with study drug (see Figure 1); however, it is necessary to interpret such subgroup analyses with caution

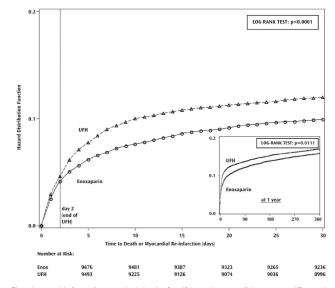
Figure 1: Relative Risks of and Absolute Event Rates for the Primary Endpoint at 30 Days in Various

			Rela	tive Risk		-	
Subgroup	No. of			i	UFH	Enox	Reduction
	Patient	\$			(%)	(%)	in Risk
Sex: Male	15696				10.1	8.2	18
Sex: Female	4783			- 1	18.3	15.4	16
Age: <75 yrs	17947				9.9	7.8	20
Age: >=75 yrs	2532				26.3	24.8	6
Infarct location: Anterior	8933		-	_	14.0	12.5	11
Infarct location: Other	11400				10.2	7.9	23
Diabetes: No	17189			-	11.1	9.2	17
Diabetes: Yes	3060			-	17.1	13.6	20
Prior MI: No	17745			-	11.1	9.2	17
Prior MI: Yes	2659		<u> </u>	-	17.8	14.3	20
Fibrinolytic agent: Streptokinase	4139		<u> </u>		11.8	10.2	13
Fibrinolytic agent: Fibrin-specific	16283				12.0	9.8	18
Time to treatment: <median< td=""><td>9899</td><td></td><td></td><td></td><td>11.3</td><td>8.7</td><td>23</td></median<>	9899				11.3	8.7	23
Time to treatment: >=Median	10394			-1	12.5	11.0	12
PCI in 30 Days: No	15763			-	11.4	9.7	15
PCI in 30 Days: Yes	4716		<del>`</del>		13.9	10.8	23
Overall -	20479				12.0	9.9	17
	L	0.50	0.75	1.00	1.25	1	.50
<		Eno	xanarin better	r	UFH b	etter -	>

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% and opposing a point same of the result of the rest of the rest of the rest of the second and the rest of the rest of the second and the rest of the r (median: 3.2 hours).

The beneficial effect of enoxaparin on the primary endpoint observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2).

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



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 continuation. These results provide evidence that UFH was effective and that it would be better if used onger than 48 hours. There is a similar increase in endpoint event rate when enoxaparin was discon suggesting that it too was discontinued too soon in this study.

The rates of major hemorrhages (defined as requiring 5 or more units of blood for transfusion, or 15% drop in hematocrit or clinically overt bleeding, including intracranial hemorrhage) at 30 days were 2.1% in the enoxaparin group and 1.4% in the unfractionated heparin group. The rates of intracranial hemorrhage at 30 days were 0.8% in the enoxaparin group and 0.7% in the unfractionated heparin group. The 30-day rate of the composite endpoint of death, myocardial re-infarction or ICH (a measure of net clinical benefit) was

Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection

The Enoxaparin Sodium Injection, USP prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection (see Dosage and Administration (2) and How Supplied/Storage and Handling (16)].

#### 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Actio

Enoxaparin is a low molecular weight heparin which has antithrombotic properties

#### 12.2 Pharmacodynamics

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

A<sub>max</sub> (IU/mL or ∆ sec)

(h\*IU/mL or h\* ∆ sec)

<sup>†</sup> Median (range)

Distribution

Elimination

 $\mathbf{t}_{max}^{\dagger}(h)$ 

AUC (ss

Pharmacokinetic trials were conducted using the 100 mg/mL formulation. Maximum anti-Factor Xa and antithrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcutaneous injection of enoxaparin. Mean peak anti-ractor had activities occur is to should also an ensure succurateous injection of encorporation wear peak anti-Factor Xa activity was 0.16 l/Jmc, (1-58 mg/mL) and 0.38 l/JmC, (1-83 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 given subcutaneously, based on anti-Factor Xa activity is approximately 100% in healthy subjects.

A 30 mg intravenous bolus immediately followed by 1 mg/kg subcutaneously every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 84% of steady-state levels. Steady state is achieved on the second day of treatment.

Enoxaparin pharmacokinetics appears to be linear over the recommended dosage rate 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 ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose tics. After repe ated subcutaneous administration of the 1 mg/kg twice-daily regime state is reached from day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

Although not studied clinically, the 150 mg/mL concentration of enoxaparin sodium is projected to result in anticoagulant activities similar to those of 100 mg/mL and 200 mg/mL concentrations at the same enoxaparin dose. When a daily 1.5 mg/kg subcutaneous injection of enoxaparin sodium was given to 25 healthy male and female subjects using a 100 mg/mL or a 200 mg/mL concentration the following pharmacokinetic profiles were obtained (see Table 13).

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

1.37 (±0.23)

1.45 (±0.22)

102% to 110%

3 (2 to 6)

3.5 (2 to 6)

14.26 (±2.93)

15.43 (±2.96)

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

Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower

90% CI 105% to 112%

Anti-lla

0.23 (±0.05)

0.26 (±0.05)

4 (2 to 5)

4.5 (2.5 to 6)

1.54 (±0.61)

1.77 (±0.67)

Hepte

102% to 111%

1321 (±219)

1401 (±227)

103% to 109%

3.3 (2 to 5) 3 (2 to 5)

Concentration Anti-Xa

100 mg/mL

200 mg/mL

90% CI

100 mg/mL

200 mg/mL

100 mg/mL

200 mg/mL

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

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

		p value ve
est	aPTT	<sup>§</sup> CL = Conf

Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium 30 mg every 12 hours subcutaneously in patients undergoing elective knee replacement surgery was compared to heparin 5,000 U every 8 hours subcutaneously. A total of 453 patients were randomized in the study and all were 111 (±17) 22 (±7) 2.5 (2 to 4.5) 3 (2 to 4.5)

was lower for enoxaparin sodium compared to heparin

#### Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

provided below (see Table 19).

	Post-discharge	Oosing Regimen
Indication (Post Discharge)	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Placebo daily subcutaneously n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Treatment Failures Total DVT (%)	6 (7)* (95% Cl <sup>†</sup> : 3 to 14)	18 (20) (95% CI: 12 to 30)
Proximal DVT (%)	5 (6) <sup>±</sup> (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)

## p value versus placebo = 0.008 CI= Confidence Interval

<sup>‡</sup> 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 regir of either enoxaparin sodium 40 mg (n=131) once a day subcutaneously or to placebo (n=131) for 3 weeks. A

a maximal duration of 8 days of therapy. The combined incidence of the triple endpoint of death, myoca 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).

Table 23: Efficacy of Enoxaparin Sodium in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (combined endpoint of death, myocardial infarction, or recurrent angina)

	Dosing Re	Dosing Regimen*		
	Enoxaparin Sodium 1 mg/kg q12h subcutaneous	Heparin aPTT Adjusted Intravenous	Reduction (%)	<u>p Value</u>
Indication	n (%)	Therapy n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Time point <sup>†</sup> 48 Hours	96 (6.1)	112 (7.3)	1.2	0.120
14 Days	261 (16.5)	303 (19.8)	3.3	0.017
30 Days	313 (19.8)	358 (23.4)	3.6	0.014

Evaluation time points are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days). 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)

	Dosing Re	Dosing Regimen*		
Indication	Enoxaparin Sodium 1 mg/kg q12h subcutaneously n (%)	Heparin aPTT Adjusted Intravenous Therapy n (%)	Reduction (%)	<u>p Value</u>
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Time point <sup>†</sup> 48 Hours 14 Days	16 (1.0) 76 (4.8)	20 (1.3) 93 (6.1)	0.3	0.126
30 Days	96 (6.1)	118 (7.7)	1.6	0.069

All patients were also treated with aspirin 100 to 325 mg per day

<sup>†</sup> 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 (32.0% 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).

#### 14.6 Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

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 4,000 U) and followed with an infusion of 12 U/kg per hour (initial maximum 1,000 U per hour) that was diguisted to maintain an aPTT of 1.5 to 2 times the control value. The intravenous infusion 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 creatining clearance of less than 30 mL per minute), the dose was to be modified 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 for enoxaparin was 6.6 days. The mean treatment duration of unfractionated heparin was 54 hours.

All patients were treated with aspirin for a minimum of 30 days. Eighty percent of patients received a fibrin-specific agent (19% tenecteplase, 5% reteplase and 55% alteplase) and 20% received streptokinase.

distribution was: 87% Caucasian, 9.8% Asian, 0.2% Black, and 2.8% other. Medical history included previous MI (13%), hypertension (44%), diabetes (15%) and angiographic evidence of CAD (5%). Concomitant medication included aspirin (95%), beta-blockers (86%), ACE inhibitors (78%), statins (70%) and clopidogrel (27%). The MI at entry was anterior in 43%, non-anterior in 56%, and both in 1%.

The primary efficacy endpoint was the composite of death from any cause or myocardial re-infarction in the

10.1%) as compared to the heparin group (12.2%)

#### HOW SUPPLIED/STORAGE AND HANDLING 16

Enoxaparin Sodium Injection, USP is supplied in two concentrations as follows:						
	100 mg per mL Concentration					
NDC	Strength*	Anti-Xa Activity <sup>†</sup>	Label Color	Package Factor		
71288 <b>-410-</b> 81	30 mg per 0.3 mL Single-Dose Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	3,000 IU	Light Blue	10 syringes per carton		
71288 <b>-410-</b> 83	40 mg per 0.4 mL Single-Dose Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	4,000 IU	Yellow	10 syringes per carton		
71288 <b>-410-</b> 85	60 mg per 0.6 mL Single-Dose Graduated Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	6,000 IU	Orange	10 syringes per carton		
71288 <b>-410-</b> 87	80 mg per 0.8 mL Single-Dose Graduated Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	8,000 IU	Brown	10 syringes per carton		
71288 <b>-410-</b> 89	100 mg per mL Single-Dose Graduated Prefilled Syringe	10,000 IU	Gray	10 syringes per carton		

with Automatic Safety Device<sup>‡</sup>

Strength represents the number of milligrams of enoxaparin sodium in Water for Injection, Enoxaparin Sodium bierign representation for the number of the strange of the strang

Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Hepain Reference Standard. Each Enoxaparin Sodium Injection, USP prefilled syringe is for single, one-time use only and is affixed with

a 27 gauge x 1/2 inch needle

#### 150 mg per mL Concentration

NDC	Strength*	Anti-Xa Activity <sup>†</sup>	Label Color	Package Factor
	120 mg per 0.8 mL Single-Dose Graduated Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	12,000 IU	Purple	10 syringes per carton
	150 mg per mL Single-Dose Graduated Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	15,000 IU	Navy Blue	10 syringes per carton
* Strength represents	the number of milligrams of enoxapa	arin sodium in	Water for Injec	tion. Enoxaparin Sodium

Injection, USP 120 mg 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 Heprix Reference Standard. Heparin Reference Standard. <sup>1</sup> Each Enoxaparin Sodium Injection, USP graduated prefilled syringe is for single, one-time use only and is affixed

with a 27 gauge x 1/2 inch needle.

Storage Conditions

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature.1

#### WARNING: Keep out of the reach of children

Sterile, Nonpyrogenic, Preservative-free, PVC-free, DEHP-free. The container closure is not made with natural rubber latex.

#### PATIENT COUNSELING INFORMATION

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs, platelet inhibitors, or other anticoagulants, advise them to watch for signs and symptoms of spinal or epidural hematoma, such as tingling, numbness (especially in the lower limbs) and muscular weakness. Instruct the patient to seek immediate medical attention if any of these symptoms occur.

Inform patients:

- of the instructions for injecting enoxaparin sodium 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 thrombocytopenia (such as a rash of dark red spots under the skin) to their physician [see Warnings and Precautions (5.1, 5.5)].
- 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 Marrison and Decordings (5.4.5.2)] Warnings and Precautions (5.1, 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)].

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When percutaneous coronary intervention was performed during study medication period, patients received antithrombotic support with blinded study drug. For patients on enoxaparin, the PCI was to be performed on enoxaparin (no switch) using the regimen established in previous studies, i.e. no additional dosing, if the last subcutaneous administration was less than 8 hours before balloon inflation, intravenous bolus of 0.3 mg/kg enoxaparin if the last subcutaneous administration was more than 8 hours before balloon inflation

Among 20,479 patients in the ITT population, the mean age was 60 years, and 76% were male. Racial

first 30 days after randomization. Total follow-up was one year.

The rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, and 12% in the unfractionated heparin group, a 17% reduction in the relative risk, (P=0.000003) (see Table 25).

Apparent clearance and A<sub>max</sub> derived from anti-Factor Xa values following single and multiple subcutaneous dosing in geriatric subjects were close to those observed in young subjects.

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

has not been conclusively identified; however, body weight may be a contributing factor.

CI = Confidence Interva versus placebo = 0.013 fidence Limit 105 (±17) 19 (±5)

All Treated Total Knee Replacement Patients

treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.6% others.

Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis

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 enoxparin sodium 40 mg (n=90) once a day subcutaneously or to placebo (n=89) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 69.4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo. The efficacy data are

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

	Post-discharge	Post-discharge Dosing Regimen			
dication (Post Discharge)	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Placebo daily subcutaneously n (%)			
Il Treated Extended Prophylaxis Patients	90 (100)	89 (100)			
reatment Failures Total DVT (%)	6 (7)* (95% Cl <sup>†</sup> : 3 to 14)	18 (20) (95% CI: 12 to 30)			

# molecular weight species with much reduced biological potency. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments

### Special Populations Gender Apparent clearance and $A_{max}$ derived from anti-Factor Xa values following single subcutaneous dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters

Geriatric

40% of the dose.

Metabolism

## Following intravenous dosing, the total body clearance of enoxaparin is 26 mL/min. After intravenous dosing of enoxaparin labeled with the gamma-emitter, <sup>99m</sup>Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after a single subcutaneous dose to about 7 hours after repeated dosing. Significant anti-Factor Xa activity persists in plasma for about 12 hours following a 40 mg subcutaneous once a day dose.

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENOXAPARIN SODIUM INJECTION safely and effectively. See full prescribing information for ENOXAPARIN SODIUM INJECTION.

ENOXAPARIN SODIUM injection, for subcutaneous and intravenous use

## Initial U.S. Approval: 1993

#### WARNING: SPINAL/EPIDURAL HEMATOMAS See full prescribing information for complete boxed warning

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecula veight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider hese risks when scheduling patients for spinal procedures. Factors that can increase the risk or leveloping 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 antiinflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery
- Optimal timing between the administration of enoxaparin sodium injection and neuraxia
- procedures is not known Ionitor patients frequently for signs and symptoms of neurological impairment. If neurologica
- compromise is noted, urgent treatment is necessary. (5.1, 7)

### -- INDICATIONS AND USAGE-

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

## --- DOSAGE AND ADMINISTRATION

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

#### FULL PRESCRIBING INFORMATION: CONTENTS\* WARNING: SPINAL/EPIDURAL HEMATOMAS

#### INDICATIONS AND USAGE

- Prophylaxis of Deep Vein Thrombosis 1.1
- Treatment of Acute Deep Vein Thrombosis
- 1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial
- 1.4
- Treatment of Acute ST-Segment Elevation Myocardial Infarction
- DOSAGE AND ADMINISTRATION Pretreatment Evaluation 2.1
- 2.2 Adult Dosage
- 2.3 Dose Reduction for Patients with Severe Renal Impairment
- 2.4 Recommended Dosage for Geriatric Patients with Acute ST-Segment Elevation Myocardial
- Infarction 2.5 Administration
- 2.6 Monitoring for Safety
- DOSAGE FORMS AND STRENGTHS
- 3 4 CONTRAINDICATIONS

### WARNINGS AND PRECAUTIONS

- 5.1 Increased Risk of Hemorrhage
- Increased Risk of Bleeding following Percutaneous Coronary Revascularization Procedures 5.2
- Increased Risk of Bleeding in Patients with Concomitant Medical Conditions 5.3
- 5.4 Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis
- 5.5 Thrombocytopenia
- 5.6 Interchangeability with other Heparins
- Increased Risk of Thrombosis in Pregnant Women with Mechanical Prosthetic Heart Valves 5.7
- ADVERSE REACTIONS
- Clinical Trials Experience 6.1
- 62 Postmarketing Experience

6

- DRUG INTERACTIONS

#### FULL PRESCRIBING INFORMATION

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

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery
- Optimal timing between the administration of enoxaparin sodium injection and neuraxia procedures is not known
- Monitor patients frequently for signs and symptoms of neurological impairment. If neur 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

1 INDICATIONS AND USAGE

- 1.1 Prophylaxis of Deep Vein Thrombosis
- Enoxaparin Sodium Injection is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE)
- · in patients undergoing abdominal surgery who are at risk for thromboembolic complications [see Clinical Studies (14.1)
- in patients undergoing hip replacement surgery, during and following hospitalization
- · in patients undergoing knee replacement surgery
- in medical patients who are at risk for thromboembolic complications due to severely restricted
- mobility during acute illness

## 1.2 Treatment of Acute Deep Vein Thrombos

- Enoxaparin Sodium Injection is indicated for: the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium
- the outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium
- 1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial

#### -DOSAGE FORMS AND STRENGTHS 100 mg per mL concentration (3):

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

5

5.1

WARNINGS AND PRECAUTIONS

may not prevent or reverse neurological sequelae.

hematocrit or blood pressure should lead to a search for a bleeding site

5.2 Increased Risk of Bleeding following Percutaneous Coronary Revas

5.3 Increased Risk of Bleeding in Patients with Concomitant Medical Conditions

5.4 Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis

benefit-risk assessment and after non-heparin alternative treatments are considered.

Thrombocytopenia can occur with the administration of enoxaparin sodium.

Circulating antibodies may persist for several years.

cases have been fata

The site of the procee Administration (2.1)].

5.5 Thrombocytopenia

lacebo in clinical trial

6

enoxaparin sodium should be discontinued.

ADVERSE REACTIONS

6.1 Clinical Trials Experience

subcutaneously.

hage

not reflect the rates observed in clinical practice.

5.6 Interchangeability with other Heparins

hemorrhage.

Cases of epidural or spinal hemorrhage and subsequent hematomas have been reported with the use of enoxaparin sodium injection and epidural or spinal anesthesia/analgesia or spinal puncture procedures,

resulting in long-term or permanent paralysis. The risk of these events is higher with the use of postoperative

Indivelling 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 injection and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium injection [see Clinical Pharmacology (11.3)]. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticcagulant effect of enoxaparin sodium injection

is low: however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Placement or removal of a catheter should be delayed for at least 12 hours after administration of lowe

doses (30 mg once or twice daily or 40 mg once daily) of enoxaparin sodium injection and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of enoxaparin sodium injection. Anti-Xa levels are still detectable at these time points, and these delays are

To a guarantee that neuraxial hematoma will be avoided. Patients receiving the 0.75 mg/sg twice-daily dose or the 1 mg/kg twice-daily dose should not receive the second enoxaparin sodium injection dose in the twice-daily regime to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent enoxaparin sodium injection dose after catheter removal cannot

be made, consider delaying this next dose for at least 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

Considering both mark for uncess and uncess and uncess to becamp in the contract of the proceeding and patient risk factors. For patients with creatinine clearance <30 mL/minute, additional considerations are necessar because elimination of enoxaparin sodium injection is more prolonged; consider doubling the timing o removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin sodium injection (30 m 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 (numbeness or weakness in

lower limbs), and bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience

any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent

Use enoxaparin sodium injection with extreme caution in conditions with increased risk of hemorrhage, such

as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly 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

Bleeding can occur at any site during therapy with enoxaparin sodium injection. An unexplained fall in

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between encoxpaprin sodium injection does. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be

removed immediately. If a manual compression method is used, sheath should be removed 6 hours after

the last intravenous/subcutaneous enoxaparin sodium injection. If the treatment with enoxaparin sodium is

to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation [see Dosage and

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

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

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

Only use enoxaparin sodium in patients with a history of HIT if more than 100 days have elapsed since

the prior HIT episode and no circulating antibodies are present. Because HIT may still occur in these

circumstances, the decision to use enoxaparin sodium in such a case must be made only after a careful

Moderate thrombocytopenia (platelet counts between 100,000/mm<sup>3</sup> and 50,000/mm<sup>3</sup>) occurred at a rate

of 1.3% in patients given enoxaparin sodium, 1.2% in patients given heparin, and 0.7% in patients given

. Platelet counts less than 50,000/mm<sup>3</sup> occurred at a rate of 0.1% in patients given enoxaparin sodium, in 0.2%

of patients given heparin, and 0.4% of patients given placeho in the same trials. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm<sup>3</sup>,

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.

Use of enoxaparin sodium injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves may result in valve thrombosis. In a clinical study of pregnant women with mechanical prosthetic

heart valves given enoxaparin sodium injection (1 mg/kg twice daily) to reduce the risk of thromboembolism The art valves given encodening including including where a compared any to reduce the risk of minimolentitorism. 2 of 8 women developed chits resulting in blockage of the valve and leading to maternal and fetal death. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving encodapair sodium injection for thrombosorphylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thrombosembolism during pregnancy and, when pregnant, have a higher rate of fetal loss and the prostant source the source of the prostant source of the pr

from stillbirth, spontaneous abortion, and premature delivery. Therefore, frequent monitoring of peak and

trough anti-Factor Xa levels, and adjusting of dosage may be needed [see Use in Specific Populations (8.6)]

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

During clinical development for the approved indications, 15,918 patients were exposed to enoxaparin sodium. These included 1,228 for prophylaxis of deep vein thrombosis following abdominal surgery in patients at risk for thromboembolic complications, 1,368 for prophylaxis of deep vein thrombosis following

parents at now to introduce induct complications, 1,360 for pophylaxis of deep vein thioritosis biolowing 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 addeminal 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

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

• Increased Risk of Hemorrhage [see Warnings and Precautions (5.1)]

Thrombocytopenia [see Warnings and Precautions (5.5)]

• Spinal/epidural hematomas [see Boxed Warning and Warnings and Precautions (5.1)]

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

diagnosis and treatment including consideration for spinal cord decompression even though such treat

Increased Risk of Hemorrhage

- Single-dose graduated prefilled syringes: 120 mg per 0.8 mL, 150 mg per mL
- -- CONTRAINDICATIONS-
- Active major bleeding (4)
- History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (4)
- Hypersensitivity to enoxaparin sodium (4)
- Hypersensitivity to heparin or pork products (4)
- -- WARNINGS AND PRECAUTIONS Increased Risk of Hemorrhage: Monitor for signs of bleeding. (5.1, 5.2, 5.3)
- Risk of Heparin-Induced Thrombocytopenia with or without Thrombosis. (5.4)
- Thrombocytopenia: Monitor platelet count closely. (5.5)
- Interchangeability with other heparins: Do not exchange with heparin or other LMWHs. (5.6)
- Increased Risk of Thrombosis in Pregnant Women with Mechanical Prosthetic Heart Valves: Women and their fetuses may be at increased risk. Monitor more frequently and adjust dosage as needed. (5.7) ----- ADVERSE REACTIONS -----

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

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

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

- ---- USE IN SPECIFIC POPULATIONS --
- Severe Renal Impairment: Adjust dose for patients with creatinine clearance <30 mL/min. (2.3, 8.7)
- Geriatric Patients: Monitor for increased risk of bleeding. (8.5) Low-Weight Patients: Observe for signs of bleeding. (8.8)
- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
- Revised: 07/2022
- 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy 82 Lactation 8.4 Pediatric Use 8.5 Geriatric Use 8.6 Patients with Mechanical Prosthetic Heart Valves 8.7 Renal Impairment 8.8 Low-Weight Patients 8.9 Obese Patients 10 OVERDOSAGE 11 DESCRIPTION 12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action 12.2 Pharmacodynamics 12.3 Pharmacokinetics 13 NONCLINICAL TOXICOLOGY
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

during Acute Illness

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

14.4

Infarction

2.5 Administratio

[see Dosage and Administration (2.2)].

Subcutaneous Injection Technique

abdominal wall

olume is needed to admini left in the syringe.

subcutaneous injection.

- 13.2 Animal Toxicology and/or Pharmacology
- 13.3 Reproductive and Developmental Toxicology
- CLINICAL STUDIES
- 14.1 Prophylaxis of Deep Vein Thrombosis following Abdominal Surgery in Patients at Risk for Thromboembolic Complications
- Prophylaxis of Deep Vein Thrombosis following Hip or Knee Replacement Surgery 14.2

Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

14.6 Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

Do not administer enoxaparin sodium injection by intramuscular injection.

Administer enoxaparin sodium injection by intravenous or subcutaneous injection only.

· Do not inject into skin that has bruises or scars. Do not inject through clothes

only and are available with a system that shields the needle after injection

remove by pulling on the plunger as this may damage the syringe.

Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility

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

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

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

Enoxaparin sodium injection is a colorless or light yellow transparent liquid, and as with other parenteral

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

· Position patients in a supine position for enoxaparin sodium injection administration by deep

Do not expel the air bubble from the prefilled syringes before the injection, to avoid the loss of drug.

· Alternate injection sites between the left and right anterolateral and left and right posterolateral

Enoxaparin sodium injection prefilled syringes and graduated prefilled syringes are for single, one-time use

Remove the prefilled syringe from the packaging by peeling at the arrow as directed on the lid. Do not

1. Remove the needle shield by pulling it straight off the syringe (see Figure A). If less than the full syringe

Introduce the whole length of the needle into a skin fold held between the thumb and forefinger:

hold the skin fold throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.

ster the prescribed dose, eject syringe contents until the prescribed d

drug products, should be inspected visually for particulate matter and discoloration prior to administration

Enoxaparin Sodium Injection is indicated for the prophylaxis of ischemic complications of unstable angina

#### 1.4 Treatment of Acute ST-Segment Elevation Myocardial Infarction

Enoxaparin Sodium Injection, when administered concurrently with aspirin, has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction (STEMI) receiving thrombolysis and being managed medically or with percutaneous coronary intervention (PCI)

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Pretreatment Evaluation

Evaluate all patients for a bleeding disorder before starting enoxaparin sodium injection treatment, unless

#### treatment is urgently needed. 2.2 Adult Dosage

Abdominal Surgery

The recommended dose of enoxaparin sodium injection is **40 mg** by subcutaneous injection once a day (with the initial dose given 2 hours prior to surgery) in patients undergoing abdominal surgery who are at risk for thromboembolic complications. The usual duration of administration is 7 to 10 days [see Clinical Studies (4.4.1)] (14.1)].

#### Hip or Knee Replacement Surgery

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

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

#### Medical Patients during Acute Illness

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

#### Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

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

The recommended dose of enoxaparin sodium injection is 1 mg/kg every 12 hours administered subcutaneously or 1.5 mg/kg once a day administered subcutaneously at the same time every day for inpatient (hospital) treatment of patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for period to be a subcutaneously of the same time acute deep vein thrombosis with pulmonary embolism (who are not candidates for period to be a subcutaneously of the same time acute deep vein thrombosis with acute deep vein thrombosis without pulmonary embolism (who are not candidates for period to be a subcutaneously of the same time acute deep vein thrombosis with acute deep vein thrombosis without pulmonary embolism (who are not candidates for period to be a subcutaneously of the same time acute deep vein thrombosis with acute deep vein thrombosis without pulmonary embolism (who are not candidates for period to be acuted by the same time acute deep vein thrombosis with acute deep outpatient treatment).

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

#### Unstable Angina and Non-Q-Wave Myocardial Infarction

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

#### Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

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

For patients managed with percutaneous coronary intervention (PCI), if the last enoxaparin sodium injection subcutaneous administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last enoxaparin sodium injection subcutaneous administration was given more than 8 hours before balloon inflation, administer an intravenous bolus of 0.3 mg/kg of enoxaparin sodium injection (see Warnings and Precautions (5.2)1.

#### 2.3 Dose Reduction for Patients with Severe Renal Impairment

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatining 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/m

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

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



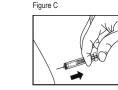
Figure A

Ŵ

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



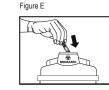
Remove the syringe from the injection site keeping your finger on the plunger rod (see Figure C). 3.



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). Figure D



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



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

· The safety system should not be sterilized. Activation of the safety system may cause minimal splatter of fluid. For optimal safety, activate the system while orienting it downwards away from yourself and others.

#### Intravenous (Bolus) Injection Technique

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

### 2.6 Monitoring for Safety

During therapy monitor complete blood counts including platelets and stool occult blood. Assess for signs and symptoms of bleeding.

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

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

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

#### 3 DOSAGE FORMS AND STRENGTHS

Enoxaparin Sodium Injection, USP is a colorless or light yellow transparent liquid available in two concentrations:

#### 100 mg per mL Concentration Single-Dose Prefilled Syringes

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

### 4 CONTRAINDICATIONS

Enoxaparin sodium is contraindicated in patients with:

Active major bleeding

- History of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies [see Warnings and Precautions (5.4)]
- Known hypersensitivity to enoxaparin sodium (e.g., pruritus, urticaria, anaphylactic/anaphylactoid reactions) [see Adverse Reactions (6.2)]
- · Known hypersensitivity to heparin or pork products

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

aparin sodium doses were a 30 mg intravenous bolus followed by 1 mg/kg every 12 hours

#### Table 2: Major Bleeding Episodes following Abdominal and Colorectal Surgery\*

	Dosing	Dosing Regimen		
Indications	Enoxaparin Sodium 40 mg daily subcutaneously	Heparin 5,000 U q8h subcutaneously		
Abdominal Surgery	n=555 23 (4%)	n=560 16 (3%)		
Colorectal Surgery	n=673 28 (4%)	n=674 21 (3%)		

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

#### Table 3: Major Bleeding Episodes following Hip or Knee Replacement Surgery\*

		Dosing Regimen		
Indications	Enoxaparin Sodium 40 mg daily subcutaneously	Enoxaparin Sodium 30 mg q12h subcutaneously	Heparin 15,000 U/24h subcutaneously	
Hip Replacement Surgery without Extended Prophylaxis <sup>†</sup>	-	n=786 31 (4%)	n=541 32 (6%)	
Hip Replacement Surgery with Extended Prophylaxis	-	-	-	
Peri-operative Period <sup>‡</sup>	n=288 4 (2%)	-	-	
Extended Prophylaxis $Period^\$$	n=221 0 (0%)	-	-	
Knee Replacement Surgery without Extended Prophylaxis <sup>†</sup>	-	n=294 3 (1%)	n=225 3 (1%)	

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

<sup>+</sup> 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

<sup>§</sup> Enoxaparin sodium 40 mg subcutaneously once a day for up to 21 days after discharge

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

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

		Dosing Regimen		
			Placebo <sup>†</sup>	
Indication	20 mg daily subcutaneously	40 mg daily subcutaneously		
Medical Patients during Acute Illness	n=351 1 (<1%)	n=360 3 (<1%)	n=362 2 (<1%)	

\* Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of 22 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

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

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

Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, 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 6: Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

	Dosing Regimen			
Indication	Enoxaparin Sodium* 1 mg/kg q12h subcutaneously	Heparin* aPTT Adjusted Intravenous Therapy		
Unstable Angina and Non-Q- Wave MI <sup>†‡</sup>	n=1578 17 (1%)	n=1529 18 (1%)		

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

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

Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥3 g/dL or transfusion of 2 or more units of blood rrhages were always considered maio products. Intraocular, retroperitoneal, and intracranial hemo

Adverse Event n (%) n (%) Atrial fibrillation 11 (0.70 3 (0.20 Heart failure 15 (0.95 11 (0.72) 11 (0.70 11 (0.72) Lung edema 13 (0.82) 9 (0.59

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

Indication

Acute ST-Segment Elevation

Major bleeding (including ICH)<sup>†</sup>

Intracranial hemorrhages (ICH)

Elevations of Serum Aminotransferases

should be interpreted with caution

Local Reactions

xaparin sodium

Adverse Reaction

Adverse Reactior

Peripheral edema

Adverse Reaction

hrombocytopenia

Adverse Reaction

Injection Site Pain

Iematuria

incidence of  $\leq 1\%$ 

Infarction

heparin.

Injection Site Hemorrhage

are provided below (see Table 12).

Dyspnea

Confusion

Diarrhea

lausea

unblinded fashion in one clinical trial.

Fever

lausea

nemia

Edema

lemorrhage

Hemorrhage

Anemia

Ecchymos

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

enoxaparin sodium group, are provided below (see Tables 8 to 11).

Undergoing Abdominal or Colorectal Surgery

Undergoing Hip or Knee Replacement Sur

to 6.1% and 5.9% of patients, respectively, during treatment with enoxaparin sodium.

**Nyocardial Infarction** 

Enoxaparin Sodium\* Initial 30 mg intravenous be

l mg/kg q12h subcuta

followed by

n=10176

n (%)

211 (2.1) 84 (0.8)

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

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels

greater than three times the upper limit of normal of the laboratory reference range have been reported in up

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

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

Other adverse reactions that were thought to be possibly or probably related to treatment with enoxaparin

sodium, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the

Table 8: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Patients

Enoxaparin Sodium

Table 9: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Patients

40 mg daily subco. n=1228 مر

Severe

Enoxaparin Sodium 40 mg daily

subcutaneous

Peri-operative Period

n=288\*

0 8

<1 13

surgery patients for up to 21 days in one clinical trial.

Patients with Severely Restricted Mobility during Acute Illness

Extende

rophylaxi

Period

n=131

0 0

0 5

0 16 0 <2 <1 2 2

0 6 0 0 <1 3 <1 4

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

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

Table 10: Adverse Reactions Occurring at >2% Incidence in Enoxaparin Sodium-Treated Medical

Enoxaparin Sodium 40 mg daily subcutaneously n=360

3.3

2.8

2.2

2.2

Table 11: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Patients Undergoing Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

Total

Adverse Events in Enoxaparin Sodium-Treated Patients with Unstable Angina or Non-Q-Wave Myocardial

Non-hemorrhagic clinical events reported to be related to enoxaparin sodium therapy occurred at an

Non-major hemorrhagic events, primarily injection site ecchymosis and hematomas, were more frequently

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

Table 12: Serious Adverse Events Occurring at ≥0.5% Incidence in Enoxaparin Sodium-Treated

Enoxaparin Sodium

1 mg/kg q12h subcutaneousl

reported in patients treated with subcutaneous enoxaparin sodium than in patients treated with intrave

Enoxaparin Sodium

1.5 mg/kg daily subcutaneously

Severe

Patients with Unstable Angina or Non-Q-Wave Myocardial Infarction

Dosing Regimen

Total

Dosing Regime

Enoxaparin Sodium 30 mg q12h

n=1080

Severe Total Severe Total Severe Total Severe Total Severe Total

<1 5

<1 4

<1 3

- <1 2 <1

Dosing Regimen

Dosing Regimen

Enoxaparin Sodium

1 mg/kg q12h

Total

3

<1

Dosing Regime

Severe

Adverse Reactions in Patients Receiving Enoxaparin Sodium for Prophylaxis or Treatment of DVT, PE

mg intravenous bol

Dosing Regime

APTT Adjusted

Intravenous Therapy

n=10151

n (%)

138 (1.4) 66 (0.7)

Heparin

n=1234

Total

6

Placebo

n=115

2

0 2

> 0 2

5 000 U q8

Severe

Heparin 5 000 U/24

n=766

<1 4 0 3

1 4 0 3

<1

5 <1 7

2

Placebo

daily subcutaneously n=362

5.2

2.8

1.1

1.7

Heparin

aPTT Adjusted

Severe

Heparin

aPTT Adjusted ous Therapy

<1

us The

rapy

Total

<1

Adverse Reactions in Enoxaparin Sodium-Treated Patients with Acute ST-Segment Elevation Myocardial

In a clinical trial in patients with acute ST-segment elevation myocardial infarction, thrombocytopenia red 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.

Possible to televely estimate their negatively of establish of details in the state televely of the state of 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 paralvsis.

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 thrombocytopenia with thrombosis [see Warnings and Precautions (5.5)] have been reported.

Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward tend reported most or most

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

Osteoporosis has also been reported following long-term therapy.

#### DRUG INTERACTIONS

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

Placental transfer of enoxaparin was observed in the animal studies. Human data from a retrospective

cohort study, which included 693 live births, suggest that enoxaparin does not increase the risk of major developmental abnormalities (see Data). Based on animal data, enoxaparin sodium injection is not predicted to increase the risk of major developmental abnormalities (see Data).

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

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 prosthetic heart valves may be at even higher risk for thrombosis [see Warnings and Precautions (5.7) and Use in Specific Populations (8.6)].

Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and

those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Pregnant women

receiving enoxaparin sodium injection 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 Warring]. 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 sodium injection is administered during pregnancy.

It is not known if monitoring of anti-Factor Xa activity and dose adjustment (by weight or anti-Factor Xa activity) of enoxaparin sodium injection affect the safety and the efficacy of the drug during pregnancy.

There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin sodium injection during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14

cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to

There have been postmarketing reports of fetal death when pregnant women received enoxaparin sodium

injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and

A clinical solution of the second sec

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). 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

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

sodium and any potential adverse effects on the breastfed child from enoxaparin sodium or from the underlying maternal condition.

the possibility of inadequate anticoagulation complicate the evaluation of these cases.

8 USE IN SPECIFIC POPULATIONS

fetal loss regardless of the type of anticoagulant used.

#### 8.1 Pregnancy

Clinical Considerations

Data

Human Data

Animal Data

8.2 Lactation Risk Summary

pregnancy only if clearly needed.

background rates.

Risk Summary

#### 8.4 Pediatric Use

Safety and effectiveness of enoxanarin sodium in nediatric natients have not been established Enoxaparin sodium is not approved for use in neonates or infants.

#### 8.5 Geriatric Use

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

Over 2800 patients, 65 years and older, have received enoxaparin sodium in clinical trials. The efficacy of Over 2000 patients, 65 years and outer, have received enoxaparin solutin in clinical infast, nee enoxaparin sodium in the enicacy of enoxaparin sodium in the genaritor (<265 years), as similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between genaritic 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 genaritic patients as compared to younger patients when enoxaparin vas administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk for enoxaparin the incidence 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 encomparins out motivation reports) has not revealed additional differences in the safety of encomparins sodium between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Encomparine for the used with care in geriatric patients who may show delayed elimination of encomparin. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered [see Warnings and Precautions (2.6) and Clinical Pharmacology (12.3)].

#### Treatment of Acute ST-Segment Elevation Myocardial Infarction

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

#### 8.6 Patients with Mechanical Prosthetic Heart Valves

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

#### 8.7 Renal Impairment

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

#### 8.8 Low-Weight Patients

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). Observe low-weight patients frequently for signs and symptoms of bleeding [see Clinical Pharmacology (12.3)].

#### 8.9 Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses of enoxaparin sodium in obese patients (BMI >30 kg/m<sup>2</sup>) has not been fully determined and there is no consensus for dose adjustment. Observe these patients carefully for signs and symptoms of thromhoembolism

#### 10 OVERDOSAGE

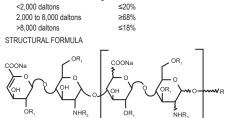
Accidental overdosage following administration of enoxaparin sodium may lead to hemorrhagic complications. Injected enoxaparin sodium may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of enoxaparin sodium injected: 1 mg protamine sulfate should be administered to neutralize 1 mg enoxaparin sodium, if enoxaparin sodium may be administered if neoxaparin sodium was administered greater than 8 hours of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours is the transmission of 0.5 mg protamine sulfate should be addinated that see the solution of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours is the solution of 0.5 mg protamine per the solution of 0.5 mg protamine per 1 mg of enoxaparin sodium was be administered if enoxaparin sodium was administered greater than 8 hours is the solution of 0.5 mg protamine per the solution of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours is the solution of 0.5 mg protamine per the solution of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours is the solution of 0.5 mg protamine per the solution of 0.5 mg per the solution of 0.5 mg per the solution o previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of enoxaparin sodium may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

If at least 12 hours have elapsed since the last enoxaparin sodium injection, protamine administration may not be required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional nation consult the labeling of protamine sulfate injection products.

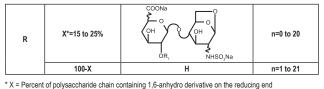
#### 11 DESCRIPTION

Enoxaparin Sodium Injection, USP is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin. The pH of the injection is 5.5 to 7.5. Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine

Intestinal mucosa, Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains a 1,6-anhydro derivative on the reducing end of the polysaccharide chain. The drug substance is the sodium salt. The average molecular weight is about 4,500 daltons. The molecular weight distribution is:



R<sub>1</sub> = H or SO<sub>3</sub>Na and R<sub>2</sub> = SO<sub>3</sub>Na or COCH.



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

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

The Enoxapain Sodium Injection, USP prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection [see Dosage and Administration (2) and How Supplied/Storage and Handling (16)].

Hepatic Impairment

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

After repeated subcutaneous 1.5 mg/kg once-daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30 to 48 kg/m<sup>3</sup>) compared to non-obese control subjects, while A<sub>m</sub> is no tincreased.

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

No pharmacokinetic interaction was observed between enoxanarin sodium injection and thrombolytics when

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of No long term atoms in terminals have been performed to be dealed and the consequences of the performance of the second se naximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m<sup>2</sup>)

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

### 13.3 Reproductive and Developmental Toxicology

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

#### 14 CLINICAL STUDIES

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

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

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

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

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

\* VTE = Venous thromboembolic events which included DVT, PE, and death considered to be nromboembolic in origin

#### CI = Confidence Interval

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

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

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

VTE = Venous thromboembolic events which included DVT, PE, and death considered to be hromboembolic in origin <sup>†</sup> CI = Confidence Interva

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

Enoxaparin sodium has been shown to reduce the risk of postoperative deep vein thrombosis (DVT) following hip or knee replacement surgery.

In a double-blind study, enoxaparin sodium 30 mg every 12 hours subcutaneously was compared to placebo in patients with hip replacement. A total of 100 patients were randomized in the study and all patients were treated. Patients ranged in age from 41 to 84 years (mean age 67.1 years) with 45% men and 55% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued to 20 with the study and the parameter of the study and all patients were treated. Patients and the study and t 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

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

#### p value versus placebo = 0.0002 p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of enoxaparin sodium in patients with hip replacement. A total of 572 patients were randomized in the study and 568 patients were treated. Patients ranged in age from 31 to 88 years (mean age 64.7 years) with 63% men and 37% women. Patients were 93% Caucasian, 6% Black, c1% Asian, and 1% others: Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The efficacy data are provided below (see Table 17). Table 17: Efficacy of Enoxaparin Sodium in the Prophylaxis of Deep Vein Thrombosis following Hip Replacement Surgery

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

		Dosing Regimen		
		Enoxaparin Sodium 20 mg daily subcutaneously	Enoxaparin Sodium 40 mg daily subcutaneously	<u>Placebo</u>
	Indication	n (%)	n (%)	n (%)
L	All Treated Medical Patients during Acute Illness	351 (100)	360 (100)	362 (100)
	Treatment Failure* Total VTE <sup>†</sup> (%)	43 (12.3)	16 (4.4)	43 (11.9)
	Total DVT (%)	43 (12.3) (95% Cl <sup>‡</sup> : 8.8 to 15.7)	16 (4.4) (95% Cl <sup>‡</sup> : 2.3 to 6.6)	41 (11.3) (95% CI <sup>‡</sup> : 8.1 to 14.6)
L	Dravimal DV/T (9/)	12 (2 7)	E (1 A)	14 (2.0)

\* Treatment failures during therapy, between Days 1 and 14

VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin

<sup>‡</sup> CI = Confidence Interval At approximately 3 months following enrollment, the incidence of venous thromboembolism remained lower in the enoxaparin sodium 40 mg treatment group versus the placebo treatment group.

#### 14.4 Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

In a multicenter, parallel group study, 900 patients with acute lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) enoxaparin sodium 1.5 mg/kg once a day subcutaneously, (ii) enoxaparin sodium 1 mg/kg every 12 hours subcutaneously, or (iii) heparin intravenous bolus (5,000 IU) followed by a continuous infusion (administered subctaneously, or (iiii) hepatin intravenous bosto (5) door (6) holiwee by a continuous intrustor administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 60.7 years) with 64.7% 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 encoaparin sodium or standard heparin therapy, and continuing for 90 days. Enoxaparin sodium or standard heparin became of canadian instant and the provided of the provided and the provided provided and the provided provided provided and the provided provid Table 21: Efficacy of Enoxaparin Sodium in Treatment of Deep Vein Thrombosis with or without

Pulmonary Embolism

		Dosing Regimen*			
	Enoxaparin Sodium 1.5 mg/kg daily subcutaneously	Enoxaparin Sodium 1 mg/kg q12h subcutaneously	Heparin aPTT Adjusted Intravenous Therapy		
Indication	n (%)	n (%)	n (%)		
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)		
Patient Outcome Total VTE <sup>†</sup> (%)	13 (4.4) <sup>‡</sup>	9 (2.9) <sup>‡</sup>	12 (4.1)		
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)		
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)		
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)		

\* 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. Outpatient exclusion criteria included the following: inability to receive excluder fiorn energy because of associated comorbid and the following, including 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 on heparin intravenous bolus (5,000 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

	Dosing	Regimen*
Indication	Enoxaparin Sodium 1 mg/kg q12h subcutaneously n (%)	Heparin aPTT Adjusted Intravenous Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome Total VTE <sup>†</sup> (%)	13 (5.3) <sup>‡</sup>	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	3 (1.2)

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

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 (5,000 U) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study, and 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 Temale and 60.0% male. Rade was distributed as tollows: 69.0% Calcasian, 4.5% 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 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 days 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).

Table 23: Efficacy of Enoxaparin Sodium in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (combined endpoint of death, myocardial infarction, Angina and Non-Q-V or recurrent angina)

Dosing Regimen*			
Enoxaparin Sodium	Heparin	Reduction	p Value
1 mg/kg q12h	aPTT Adjusted	(%)	
subcutaneously	Intravenous		

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

	Enoxaparin	UFH	Relative Risk	P Value
	Sodium Injection (N=10,256)	(N=10,223)	(95% CI)	
Outcome at 48 hours	n (%)	n (%)		
Death or Myocardial Re-infarction	478 (4.7)	531 (5.2)	0.90 (0.80 to 1.01)	0.08
Death	383 (3.7)	390 (3.8)	0.98 (0.85 to 1.12)	0.76
Myocardial Re-infarction	102 (1.0)	156 (1.5)	0.65 (0.51 to 0.84)	<0.001
Urgent Revascularization	74 (0.7)	96 (0.9)	0.77 (0.57 to 1.04)	0.09
Death or Myocardial Re-infarction or				
Urgent Revascularization	548 (5.3)	622 (6.1)	0.88 (0.79 to 0.98)	0.02
Outcome at 8 Days				
Death or Myocardial Re-infarction	740 (7.2)	954 (9.3)	0.77 (0.71 to 0.85)	<0.001
Death	559 (5.5)	605 (5.9)	0.92 (0.82 to 1.03)	0.15
Myocardial Re-infarction	204 (2.0)	379 (3.7)	0.54 (0.45 to 0.63)	<0.001
Urgent Revascularization	145 (1.4)	247 (2.4)	0.59 (0.48 to 0.72)	<0.001
Death or Myocardial Re-infarction or				
Urgent Revascularization	874 (8.5)	1181 (11.6)	0.74 (0.68 to 0.80)	<0.001
Outcome at 30 Days				
Primary efficacy endpoint				
(Death or Myocardial Re-infarction)	1017 (9.9)	1223 (12.0)	0.83 (0.77 to 0.90)	0.000003
Death	708 (6.9)	765 (7.5)	0.92 (0.84 to 1.02)	0.11
Myocardial Re-infarction	352 (3.4)	508 (5.0)	0.69 (0.60 to 0.79)	<0.001
Urgent Revascularization Death or Myocardial Re-infarction or	213 (2.1)	286 (2.8)	0.74 (0.62 to 0.88)	<0.001
Urgent Revascularization	1199 (11.7)	1479 (14.5)	0.81 (0.75 to 0.87)	<0.001

Note: Urgent revascularization denotes episodes of recurrent myocardial ischemia (without infarction) leading to the clinical decision to perform coronary revascularization during the same hospitalization. Cl denotes confidence intervals.

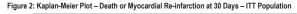
The beneficial effect of enoxaparin sodium injection on the primary endpoint was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prime was consistent autoes as fibrinolytic agent administered, and time to treatment with study drug (see Figure 1); however, it is necessary to interpret such subgroup analyses with caution.

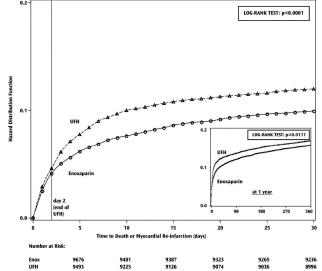
Figure 1: Relative Risks of and Absolute Event Rates for the Primary Endpoint at 30 Days in Various

<		Enox	aparin bett	er	UFH b	etter	>
		0.50	0.75	1.00	1.25	1.5	50
Overall	20479		•	-	12.0	9.9	17
PCI in 30 Days: Yes	4716		<u> </u>	-	13.9	10.8	23
,	15763		-•	-	11.4	9.7	15
Time to treatment: >=Median	10394		_	•	12.5	11.0	12
Time to treatment: <median< td=""><td>9899</td><td></td><td>-•</td><td></td><td>11.3</td><td>8.7</td><td>23</td></median<>	9899		-•		11.3	8.7	23
Fibrinolytic agent: Fibrin-specific	16283		-•-	-	12.0	9.8	18
Fibrinolytic agent: Streptokinase	4139				11.8	10.2	13
Prior MI: Yes	2659		· · · ·	-	17.8	14.3	20
Prior MI: No	17745		-•	-	11.1	9.2	17
Diabetes: Yes	3060		· · · ·	- 1	17.1	13.6	20
	17189		-•-	-	11.1	9.2	17
	11400				10.2	7.9	23
Infarct location: Anterior	8933		_	•	14.0	12.5	11
Age: >=75 yrs	2532		_	-+-	26.3	24.8	6
Age: <75 yrs	17947		-•	·	9.9	7.8	20
Sex: Female	4783				18.3	15.4	16
Sex: Male	15696		-•-	-	10.1	8.2	18
	Patient	5			(%)	(%)	in Risk
Subgroup	No. of				UFH	Enox	Reduction
			Rel	ative Risk			

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 sodium injection as compared to the unfractionated heparin (UFH) is shown at the bottom of the figure. For each subgroup, the circle is proportional to the number and represents the point estimate of the treatment effect and the horizontal lines represent the 95% confidence intervals. Fibrin-specific fibrinolytic agents included alteplase tenecteplase, and reteplase. Time to treatment indicates the time from the onset of symptoms to the administration of study drug (median: 3.2 hours).

The beneficial effect of enoxaparin sodium injection on the primary endpoint observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2)





There is a trend in favor of enoxaparin sodium injection during the first 48 hours, but most of the treatment Inference is a tartification of a recognition social methods and any and instruction of 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 sodium injection was discontinued, suggesting that it too was discontinued too soon in this study.

The rates of major hemorrhages (defined as requiring 5 or more units of blood for transfusion, or 15% drop in hematocrit or clinically overt bleeding, including intracranial hemorrhage) at 30 days were 2.1% in the enoxaparin sodium injection group and 1.4% in the unfractionated heparin group. The rates of intracranial hemorrhage at 30 days were 0.8% in the enoxaparin sodium injection group and 0.7% in the unfractionated heparin group. The 30-day rate of the composite endpoint of death, myocardial re-infarction or ICH (a

3,000 IU

4.000 IU

6 000 IU

8,000 IL

10.000 IU

Anti-Xa Activity<sup>†</sup> Label Color Package Factor

Light Blue

Yellow

Orange

Brown

Gray

10 syringes per cartor

10 syringes per carton

10 syringes per carto

10 syringes per carto

10 syringes per carton

meganin group. The 30-day rate of the composite endpoint of death, myocardian re-infarction of iCH (a measure of net clinical benefit) was significantly lower in the enoxaparin sodium injection group (10.1%) as compared to the heparin group (12.2%).

Enoxaparin Sodium Injection, USP is supplied in two concentrations (see table 26 and 27).

16 HOW SUPPLIED/STORAGE AND HANDLING

Table 26: 100 mg per mL Concentration

Strength\*

1288-432-81 30 mg per 0.3 mL Single-Dose

71288-**433-83** 40 mg per 0.4 mL Single-Dose Prefilled Syringe with Automatic Safety Device<sup>‡</sup>

71288-**434-85** 60 mg per 0.6 mL Single-Dose Graduated Prefilled Syringe with Automatic Safety Device<sup>‡</sup>

71288-436-89 100 mg per mL Single-Dose

Prefilled Syringe with Automat Safety Device<sup>‡</sup>

80 mg per 0.8 mL Single-Dose

Graduated Prefilled Syringe with Automatic Safety Device<sup>1</sup>

NDC

1288-**435-8**7

12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

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

#### 12.2 Pharmacodynamics

In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean  $\pm$ SD, 14.0 $\pm$ 3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean  $\pm$ SD, 1.22 $\pm$ 0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastir to 1.5 times the control values were seen in the informal time (11) and the activated partial tromobolisation time (aPTT). Encoxparin 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 posting-clino 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 mcg/mL) and 0.38 IU/mL (3.83 mcg/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 given subcutaneously, based on anti-Factor Xa activity is approximately 100% in healthy subjects.

A 30 mg intravenous bolus immediately followed by 1 mg/kg subcutaneously every 12 hours provided initial peak anti-factor Xa levels of 1.16 IU/Im. (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 and Administration (2)). After repeated subcutaneous administration or 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 ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics. After repeated subcutaneous administration of the 1 mg/kg twice-daily regimen, the steady state is reached from day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

Although not studied clinically, the 150 mg/mL concentration of enoxaparin sodium is projected to result in anticoagulant activities similar to those of 100 mg/mL and 200 mg/mL concentrations at the same enoxaparin dose. When a daily 1.5 mg/kg subcutaneous injection of enoxaparin sodium was given to 25 healthy male and female subjects using a 100 mg/mL or a 200 mg/mL concentration the following pharmacokinetic profiles were obtained (see Table 13).

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

•		-			
	Concentration	Anti-Xa	Anti-lla	Heptest	aPTT
A <sub>max</sub>	100 mg/mL	1.37 (±0.23)	0.23 (±0.05)	105 (±17)	19 (±5)
(IU/mL or $\Delta$ sec)	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	111 (±17)	22 (±7)
	90% CI	102% to 110%		102% to 111%	
$\mathbf{t}_{max}^{\dagger}(\mathbf{h})$	100 mg/mL	3 (2 to 6)	4 (2 to 5)	2.5 (2 to 4.5)	3 (2 to 4.5)
	200 mg/mL	3.5 (2 to 6)	4.5 (2.5 to 6)	3.3 (2 to 5)	3 (2 to 5)
AUC (ss)	100 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)	
(h*IU/mL or h* $\Delta$ sec)	200 mg/mL	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)	
	90% CI	105% to 112%		103% to 109%	1

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

Median (range)

Distribution

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

#### Elimination

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

### Metabolism

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

Special Populations

#### Gender

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

Geriatric Apparent clearance and A<sub>max</sub> derived from anti-Factor Xa values following single and multiple subcutaneous

Adding in generatic subjects were close to how any sector ad values howing angle and multiple subcatality and dosing in generatic subjects. Following once a day subcutaneous dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value [see Dosage and Administration (2.4) and Use in Specific Populations (8.5)].

#### Renal Impairment

A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady state A linear reliatorising between anti-ractor Xa plasma clearance and creatinine clearance as gleady state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady state, is marginally increased in patients with creatinine clearance 50 to 80 mL/min and patients with creatinine clearance 310 to 50 mL/min after repeated subcutaneous 40 mg once-daily doses. In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC at steady state is significantly increased on average by 65% after clearance <30 mL/min), the AUC at steady state is significantly increased on average by 65% after clearance <30 mL/min). repeated subcutaneous 40 mg once-daily doses [see Dosage and Administration (2.3) and Use in Specific Populations (8,7)1

#### Hemodialysis

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

	Dosing Regimen				
Indication	10 mg daily subcutaneously n (%)	30 mg q12h subcutaneously n (%)	40 mg daily subcutaneously		
Indication	f1 (%)	II (%)	n (%)		
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)		
Treatment Failures Total DVT (%)	40 (25)	22 (11)*	27 (14)		
Proximal DVT (%)	17 (11)	8 (4) <sup>†</sup>	9 (5)		

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

<sup>1</sup> p value versus enoxaparin sodium 10 mg once a day = 0.0168 There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens. In a double-blind study, enoxaparin sodium 30 mg every 12 hours subcutaneously was compared to placebo in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the study and 131 patients were treated, of which 99 had total knee replacement and 32 had either 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 Total Knee Replacement Surgery

	Dosing F	Regimen
Indication	Enoxaparin Sodium 30 mg q12h subcutaneously n (%)	Placebo q12h subcutaneously n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures Total DVT (%)	5 (11)* (95% Cl <sup>†</sup> : 1 to 21)	32 (62) (95% CI: 47 to 76)
Proximal DVT (%)	0 (0) <sup>‡</sup> (95% Upper CL <sup>§</sup> : 5)	7 (13) (95% CI: 3 to 24)

p value versus placebo = 0.0001

CI = Confidence Interval p value versus placebo = 0.013

CL = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study, enoxaparin sodium 30 mg every 12 Additionary, in an open rade, paramet globp, randomized damical study, encodpaint solution so unit of the parameter of the study and a study encodpaint solution solution and the parameter freated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.6% others.

Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was lower for enoxaparin sodium compared to heparin.

Extended Prophylaxis of Deep Vein Thrombosis following Hip Replacement Surgery

subcutaneously or to placebo (n=89) for 3 weeks. A total of 179 patients were randomized in the doublebilling phase of the study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 63,4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo. The efficacy data are provided below (see Table 19).

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

	Post-discharge Dosing Regimen				
Indication (Post Discharge)	Enoxaparin Sodium 40 mg daily subcutaneously n (%)	Placebo daily subcutaneously n (%)			
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)			
Treatment Failures Total DVT (%)	6 (7)* (95% Cl <sup>†</sup> : 3 to 14)	18 (20) (95% CI: 12 to 30)			
Proximal DVT (%)	5 (6) <sup>‡</sup> (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)			

#### p value versus placebo = 0.008

CI= Confidence Interval

p value versus placebo = 0.537 <sup>+</sup> 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 8 [6%] versus placebo 28 [27]; [p=<0.001).</p> [6%] versus placebo 28 [21%]; p=<0.001)

#### 14.3 Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility during Acute Illness

In a double blind multicenter, parallel group study, enoxaparin sodium 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 arthritic episodes of the lower extremities). A total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged in age from 40 to 97 years (mean

Indication	n (%)	Therapy n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)	-	-
Time point <sup>†</sup> 48 Hours	96 (6.1)	112 (7.3)	1.2	0.120
14 Days	261 (16.5)	303 (19.8)	3.3	0.017
30 Days	313 (19.8)	358 (23.4)	3.6	0.014

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

	Dosing Re			
Indication	Enoxaparin Sodium 1 mg/kg q12h subcutaneously n (%)	<u>Heparin</u> aPTT Adjusted Intravenous Therapy n (%)	Reduction (%)	<u>p Value</u>
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Time point <sup>†</sup> 48 Hours	16 (1.0)	20 (1.3)	0.3	0.126
14 Days	76 (4.8)	93 (6.1)	1.3	0.115
30 Days	96 (6.1)	118 (7.7)	1.6	0.069

#### 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

sodium versus heparin (32.0% vs 35.7%).

compared to the heparin group, 6.3% compared to 8.2% at 30 days (p=0.047).

In a multicenter, double-blind, double-dummy, parallel-group study, patients with acute ST-segment elevation vocardial 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 injection o unfractionated heparin.

Study medication was initiated between 15 minutes before and 30 minutes after the initiation of fibrinolytic Herapy. Unfact the simulated between 1's ministered beginning with an intravenous block of 60 U/kg (maximum 4,000 U) and followed with an infusion of 12 U/kg per hour (initial maximum 1,000 U per hour) that was adjusted to maintain an aPTT of 1.5 to 2 times the control value. The intravenous infusion was to be given for at least 48 hours. The enoxaparin sodium injection dosing strategy was adjusted according to the patient's age and renal function. For patients younger than 75 years of age, enoxaparin sodium injection 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 modified to 1 mg/kg every 24 hours. The subcutaneous injections of enoxaparin sodium injection were given until benefit diverger of fear a maximum of eight daw. (which bener grame first). The more treatment duration for hospital discharge or for a maximum of eight days (whichever came first). The mean treatment duration for enoxaparin sodium injection was 6.6 days. The mean treatment duration of unfractionated heparin was 54

When percutaneous coronary intervention was performed during study medication period, patients received When perculateous contraity intervention was performed during study medication period, parentis received antithromobiotic support with binded study drug. For patients on enxyaprin sodium injection, the PCI was to be performed on enxaparin sodium injection (no switch) using the regimen established in previous studies, i.e. no additional dosing, if the last subcutaneous administration was less than 8 hours before balloon inflation, intravenous bolus of 0.3 mg/kg enxaparin sodium injection if the last subcutaneous administration was more than 8 hours before balloon inflation.

All patients were treated with aspirin for a minimum of 30 days. Eighty percent of patients received a fibrin-specific agent (19% tenecteplase, 5% reteplase and 55% alteplase) and 20% received streptokinase.

Among 20,479 betients in the ITT population, the mean age was 60 years, and 76% were male. Racial distribution was: 87% Caucasian, 9.8% Asian, 0.2% Black, and 2.8% other. Medical history included previous MI (13%), hypertension (44%), diabetes (15%) and angiographic evidence of CAD (5%). Concomitant medication included aspirin (95%), beta-lockers (86%), ACE inhibitors (76%), statins (70%) and clopidogrel (27%). The MI at entry was anterior in 43%, non-anterior in 56%, and both in 1%.

The primary efficacy endopint 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 sodium injection group, and 12% in the unfractionated heparin group, a 17% reduction in the relative risk, (P=0.000003) (see Table 25).

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Mfd. by Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.

ſ	NDC	Strength*	Anti-Xa Activity <sup>†</sup>	Labol Color	Dookogo Footor		
1	Table 27: 150 m	ig per mL Concentration					
1		rin Sodium Injection, USP prefille 1/2 inch needle.	d syringe is for sing	le, one-time use	e only and is affixed with		
1	<sup>†</sup> Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.						
,	* Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. Enoxaparin Sodium Injection, USP 30 mg and 40 mg prefilled syringes, and 60 mg, 80 mg, and 100 mg graduated prefilled syringes each contain 10 mg enoxaparin sodium per 0.1 mL Water for Injection.						
l		with Automatic Safety Device <sup>‡</sup>					

NDC	Strength*	Anti-Xa Activity <sup>†</sup>	Label Color	Package Factor
71288- <b>437-92</b>	120 mg per 0.8 mL Single-Dose Graduated Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	12,000 IU	Purple	10 syringes per carton
71288- <b>438-94</b>	150 mg per mL Single-Dose Graduated Prefilled Syringe with Automatic Safety Device <sup>‡</sup>	15,000 IU	Navy Blue	10 syringes per carton

Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. Enoxaparin Sodium Injection, USP 120 mg 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 Injection, USP graduated prefilled syringe is for single, one-time use only and is affixed with a 27 gauge x 1/2 inch needle.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature.] Store in the original carton or packaging until ready to use. WARNING: Keep out of the reach of children.

## Sterile, Nonpyrogenic, Preservative-free, PVC-free, DEHP-free.

The container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use)

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs, platelet inhibitors, or other anticoagulants, advise them to watch for signs and symptoms of spinal or epidural hemathoma, such as tingling, numbress (especially in the lower limbs) and muscular weakness. Instruct the patient to seek immediate medical attention if any of these symptoms occur. Inform patients

- · of the instructions for injecting enoxaparin sodium 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 thrombocytopenia (such as a rash of dark red spots under the skin) to their physician [see Warnings and Precautions (5.1, 5.5)].
- 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 (5.1, 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)].

### 

Nanjing, China 210061

Revised: July 2022 810146-00



#### 313 (19.8) 358 (23.4) 3.0 \* 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)

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)

	Dosing Ke	gimen				
Indication	Enoxaparin Sodium 1 mg/kg q12h subcutaneously n (%)	<u>Heparin</u> aPTT Adjusted Intravenous Therapy n (%)	Reduction (%)	<u>p Value</u>		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)				
Time point <sup>†</sup> 48 Hours	16 (1.0)	20 (1.3)	0.3	0.126		
14 Days	76 (4.8)	93 (6.1)	1.3	0.115		
30 Days	96 (6.1)	118 (7.7)	1.6	0.069		

combined incidence of death, myocardial infarction, or recurrent angina remained lower for enoxaparin

Urgent revascularization procedures were performed less frequently in the enoxaparin sodium group as

### 14.6 Treatment of Acute ST-Segment Elevation Myocardial Infarction

#### Single-dose prefilled syringe

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

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

Do not get rid of any air

bubble(s) in the Enoxaparin

syringe. This can lead to a loss

To avoid bruising, **do not** rub the injection site after you have

To protect from needle-stick

injuries, each prefilled syringe has a safety system that covers

the needle after injection.

Throw away (dispose of) the used Enoxaparin Sodium

Injection prefilled syringe and

use, even if there is medicine

"Step 13: Dispose of used

caps" below

left in the prefilled syringe. See

**Enoxaparin Sodium Injection** 

prefilled syringes and needle

Enoxaparin Sodium Injection is

for one time use only. Do not reuse an Enoxaparin Sodium

Injection prefilled syringe.

needle cap right away after

Sodium Injection prefilled

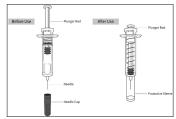
of the medicine.

injected yourself.

#### Important information:

- Your healthcare provider will tell you the prescribed dose that you should take and how often you will need to inject Enoxaparin Sodium Injection. If your dose is based on your body weight, your dose of Enoxaparin Sodium Injection might be less than what is in the prefilled syringe.
- Enoxaparin Sodium Injection is injected as a subcutaneous (under the skin) injection only. Do not inject Enoxaparin Sodium Injection into muscle
- Do not use the Enoxaparin Sodium Injection prefilled syringe if the needle cap is missing or not securely attached.
- Do not remove the needle cap until just before you give the injection.
- Do not touch the syringe plunger rod until you are ready to inject. **Do not** pull back on the plunger rod at any time.
- Storing Enoxaparin Sodium Injection prefilled syringes:
- Store Enoxaparin Sodium Injection prefilled syringes at 77°F (25°C).
- Store Enoxaparin Sodium Injection prefilled syringes in the original carton or packaging until ready to use
- Keep Enoxaparin Sodium Injection and all medicines out of the reach of children.

#### Parts of Enoxaparin Sodium Injection prefilled syringe:



#### Preparing to inject Enoxaparin Sodium Injection:

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

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

#### \*Items not included

#### Figure A



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

Step 3: Preparing a dose of Enoxaparin Sodium Injection

#### Take the prefilled syringe out of the package.

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

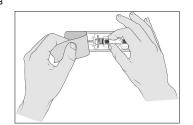
Take the prefilled syringe out of the plastic container by holding the middle of the syringe body (see Figure B).

Do not remove the prefilled syringe by pulling on the plunger rod or the needle cap as this may damage the syringe

Do not pull off the needle cap until you are ready to inject.

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

#### Figure B



Step 4: Check the Enoxaparin Sodium Injection prefilled syringe

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

#### Figure C

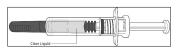
|--|

#### Step 5: Check the medicine

6

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

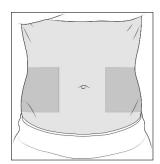
#### Figure D



#### Step 6: Choose your injection site

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

#### Figure E

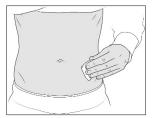


#### Step 7: Clean the injection site

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

Let your skin dry before injecting.

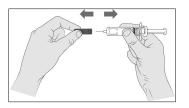
#### Figure F



#### Step 8: Remove the needle cap

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

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

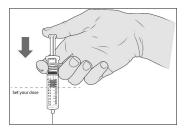


Step 9: Injecting a dose that is less than the full amount in the prefilled syringe. If your prescribed dose is the same as the amount in the prefilled syringe, go to Step 10.

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

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

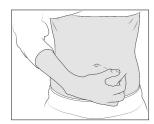
#### Figure H



#### Step 10: Injecting Enoxaparin Sodium Injection

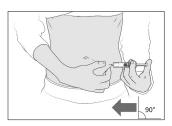
Hold the prefilled syringe like a pencil in your hand with the needle pointing down. With your other hand, pinch the cleaned stomach (abdomen) area between your forefinger and thumb to make a fold in the skin (see Figure I). Make sure you hold the skin fold during the entire injection.

#### Figure I



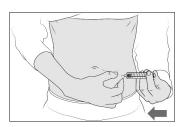
Insert the full length of the needle straight into the skin fold at about a 90° angle (see Figure J).

#### Figure J



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

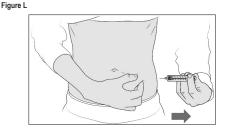
#### Figure K



#### Step 11: Remove the needle

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

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

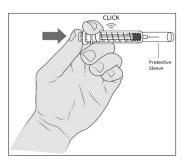


#### Step 12: Activate the safety system

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

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

#### Figure M



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

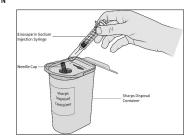
Put the used Enoxaparin Sodium Injection prefilled syringe and needle cap in an FDA-cleared sharps disposal container right away after use (see Figure N). Do not dispose of Enoxaparin Sodium Injection prefilled syringes or needle caps in your household trash.

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

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

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

#### Figure N



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

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