SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lomoh 40 (Enoxaparin Sodium Injection USP 40mg/0.4mL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per syringe:
Enoxaparin Sodium USP .....40 mg Sodium
Hydroxide USP.....q.s.
Water for Injection USP.....q.s. to 0.4 ml

3. PHARMACEUTICAL FORM

Injectable

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of Deep Vein Thrombosis
Lomoh 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.
- in patients undergoing hip replacement surgery, during and following hospitalization.
- in patients undergoing knee replacement surgery.
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Treatment of Acute Deep Vein Thrombosis Lomoh
Injection is indicated for:

- the **inpatient treatment** of acute deep vein thrombosis **with or without pulmonary embolism**, when administered in conjunction with warfarin sodium.
- the **outpatient treatment** of acute deep vein thrombosis **without pulmonary embolism**, when administered in conjunction with warfarin sodium.

Prophylaxis of Ischemic Complications of Unstable Angina and Non–Q-Wave Myocardial Infarction
Lomoh Injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

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).

4.2 Posology and method of administration

All patients should be evaluated for a bleeding disorder before administration of Lomoh Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring enoxaparin sodium activity, routine monitoring of coagulation parameters is not required (see Section 4.4).

For subcutaneous use, Lomoh Injection should not be mixed with other injections or infusions.

For intravenous use (i.e., for treatment of acute STEMI), Lomoh Injection can be mixed with normal saline solution (0.9%) or 5% dextrose in water.
Lomoh Injection is not intended for intramuscular administration.

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

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

Medical Patients During Acute Illness
In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lomoh Injection is **40 mg once a day** administered by subcutaneous injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lomoh Injection has been administered in the controlled clinical study.

Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism
In **outpatient treatment**, the patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lomoh Injection is **1 mg/kg every 12 hours** administered subcutaneously. In **inpatient (hospital) treatment**, the patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lomoh 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. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lomoh Injection). Lomoh Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2 to 3). The average duration of administration is 7 days; up to 17 days of Lomoh Injection administration has been administered in controlled clinical studies.

Unstable Angina and Non-Q-Wave Myocardial Infarction
In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lomoh Injection is **1 mg/kg** administered subcutaneously **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lomoh Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lomoh Injection has been administered in clinical studies (see Section 4.4 and 5.1)

Treatment of Acute ST-Segment Elevation Myocardial Infarction
In patients with acute ST-segment elevation myocardial infarction, the recommended dose of Lomoh 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). Dosage adjustments are recommended in patients ≥75 years of age (see Section 4.2). All patients should receive aspirin as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated.
When administered in conjunction with a thrombolytic (fibrin specific or non–fibrin specific), Lomoh Injection should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. In the pivotal clinical study, the Lomoh Injection treatment duration was 8 days or until hospital discharge, whichever came first. An optimal duration of treatment is not known, but it is likely to be longer than 8 days.

For patients managed with percutaneous coronary intervention (PCI), if the last Lomoh Injection subcutaneous administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last Lomoh Injection subcutaneous administration was given more than 8 hours before balloon inflation, an intravenous bolus of 0.3 mg/kg of Lomoh Injection should be administered (see section 4.4).

Special Populations

Hepatic Impairment

The impact of hepatic impairment on enoxaparin's exposure and antithrombotic effect has not been investigated. Caution should be exercised when administering enoxaparin to patients with hepatic impairment.

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.

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 3050 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.

In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia (see Section 4.8).

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in Table 1 (see Section 5.1 and 5.2).

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	1 mg/kg administered subcutaneously once daily
conjunction with warfarin sodium	

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)

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

Geriatric
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 injection in pivotal clinical studies. The efficacy of enoxaparin sodium injection in the geriatric (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of enoxaparin sodium injection were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when enoxaparin sodium injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of enoxaparin sodium injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving enoxaparin sodium injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin sodium injection between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Enoxaparin sodium injection 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 Section 4.4 and 5.1).

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 Section 4.2). The incidence of bleeding complications was higher in patients ≥65 years of age as compared to younger patients (<65 years).

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 Section 5.1 and 5.2)**

No dose adjustment is necessary for other indications in geriatric patients unless kidney function is impaired (see Section 4.2).

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 longterm use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see Section 4.4).

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). All such patients should be observed carefully for signs and symptoms of bleeding (see Section 5.1).

Obese Patients
Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses of enoxaparin sodium injection in obese patients (BMI >30 kg/m^2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

Method of Administration
Lomoh Injection is a clear, colorless to pale yellow solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration..
Lomoh Injection must not be administered by intramuscular injection. Lomoh Injection is intended for use under the guidance of a physician.
For subcutaneous administration, patients may self-inject only if their physicians determine that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

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

Lomoh injection prefilled syringes are for single, one-time use only and are available with a system that shields the needle after injection.

Intravenous (Bolus) Injection Technique
For intravenous injection, the multiple-dose vial should be used. Lomoh Injection should be administered through an intravenous line. Lomoh Injection should not be mixed or coadministered with other medications. To avoid the possible mixture of Lomoh Injection with other drugs, the

intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of Lomoh Injection to clear the port of drug.
Lomoh Injection may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

4.3 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 Section 4.4)
- Known hypersensitivity to enoxaparin sodium (e.g., pruritus, urticaria, anaphylactic/anaphylactoid reactions) (see section 4.8) or to any of the excipients listed in section 6.1.
- Known hypersensitivity to heparin or pork products.

4.4 Special warnings and precautions for use

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 antiinflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery

Optimal timing between the administration of enoxaparin sodium and neuraxial procedures is not known.
Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see Section 4.4 and 4.5).

Increased Risk of Hemorrhage

Cases of epidural or spinal hemorrhage and subsequent hematomas have been reported with the use of enoxaparin sodium and epidural or spinal anesthesia/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, 4.4, 4.5, and 4.8).
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 Section 5.1). Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
Placement or removal of a catheter should be delayed for at least 12 hours after administration of lower doses (30 mg once or twice daily or 40 mg once daily) of enoxaparin sodium, and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or

1.5 mg/kg once daily) of enoxaparin sodium. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial 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 next dose for at least four hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance <30 mL/minute, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin sodium (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day) (see section 5.1).
Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.
Use enoxaparin sodium 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 cases have been fatal.
Bleeding can occur at any site during therapy with enoxaparin sodium. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Percutaneous Coronary Revascularization Procedures
To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non–Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between enoxaparin sodium 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. 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 section 4.2).

Use of Lomoh Injection with Concomitant Medical Conditions
Lomoh Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage.

History of Heparin-Induced Thrombocytopenia
Use of Lomoh Injection in patients with a history of immune-mediated HIT within the past 100 days or in the presence of circulating antibodies is contraindicated (see section 4.3). Circulating antibodies may persist for several years.

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

Thrombocytopenia
Thrombocytopenia can occur with the administration of enoxaparin sodium.
Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in patients given enoxaparin sodium, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical studies.
Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given enoxaparin sodium, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same studies.
Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, Lomoh Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death (see section 4.4).

Interchangeability with Other Heparins
Lomoh Injection 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.

Pregnant Women with Mechanical Prosthetic Heart Valves
The use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion, and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed.

Laboratory Tests
Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lomoh Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of enoxaparin sodium activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of enoxaparin sodium in patients with significant renal impairment. If during enoxaparin sodium therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of enoxaparin sodium (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Whenever possible, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lomoh 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 section 4.4).

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Category B

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

Fetal Risk Summary

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

Clinical Considerations

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis (see section 4.4).

Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches (see Boxed Warning, section 4.4). Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

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

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

There have been postmarketing reports of fetal death when pregnant women received enoxaparin sodium. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been conducted (see section 4.4).

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Enoxaparin sodium has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

- Spinal/epidural hematomas (see Boxed Warning, section 4.4).
- Increased Risk of Hemorrhage (see section 4.4).
- Thrombocytopenia (see section 4.4)

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.
During clinical development for the approved indications, 15,918 patients were exposed to enoxaparin sodium. These included 1,228 for prophylaxis of deep vein thrombosis following abdominal surgery in patients at risk for thromboembolic complications, 1,368 for prophylaxis of deep vein thrombosis following hip or knee replacement surgery, 711 for prophylaxis of deep vein thrombosis in medical patients with severely restricted mobility during acute illness, 1,578 for prophylaxis of ischemic complications in unstable angina and non–Q-wave myocardial infarction, 10,176 for treatment of acute ST-elevation myocardial infarction, and 857 for treatment of deep vein thrombosis with or without pulmonary embolism. Enoxaparin sodium doses in the clinical studies for prophylaxis of deep vein thrombosis following abdominal or hip or knee replacement surgery or in medical patients with severely restricted mobility during acute illness ranged from 40 mg subcutaneously once daily to 30 mg subcutaneously twice daily. In the clinical studies for prophylaxis of ischemic complications of unstable angina and non–Q-wave myocardial infarction doses were 1 mg/kg every 12 hours and in the clinical studies for treatment of acute ST-segment elevation myocardial infarction enoxaparin sodium doses were a 30 mg intravenous bolus followed by 1 mg/kg every 12 hours subcutaneously.

Hemorrhage
The following rates of major bleeding events have been reported during clinical studies with enoxaparin sodium (see Tables below).

Table 2: Major Bleeding Episodes Following Abdominal and Colorectal Surgery*

Indications	**Dosing Regimen**	
	Enoxaparin sodium 40 mg -daily subcutaneously	**Heparin** 5000 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*

Indications	**Dosing Regimen**		
	Enoxaparin sodium 40 mg daily subcutaneously	**Enoxaparin sodium** 30 mg q12h subcutaneously	**Heparin** 15,000 U/24h subcutaneously
Hip Replacement Surgery without Extended Prophylaxis†		n=786 31 (4%)	n=541 32 (6%)

Hip Replacement Surgery with Extended Prophylaxis			
Peri-operative Period‡	n=288 4 (2%)		
Extended Prophylaxis Period§	n=221 0 (0%)		
Knee Replacement Surgery without Extended Prophylaxis†		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 studies, 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

§ 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 studies. 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***

Indication	**Dosing Regimen**		
	Enoxaparin sodium † 20 mg daily subcutaneously	**Enoxaparin sodium** † 40 mg daily subcutaneously	**Placebo**†
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 ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the study.

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

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

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

Indication	**Dosing Regimen**	
	~~Enoxaparin sodium~~ * 1 mg/kg q12h subcutaneously	**Heparin*** aPTT Adjusted Intravenous Therapy
Unstable Angina and Non–Q- Wave MI†, ‡	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 products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

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

	Dosing Regimen	
Indication	**~~Enoxaparin sodium~~ *** Initial 30 mg intravenous bolus followed by 1 mg/kg q12h subcutaneously	**Heparin*** aPTT Adjusted Intravenous Therapy
Acute ST-Segment Elevation Myocardial Infarction	n=10176 n (%) 211 (2.1)	n=10151 n (%) 138 (1.4)
Major bleeding (including ICH) †	84 (0.8)	66 (0.7)
Intracranial hemorrhages (ICH)		

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

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

Elevations of Serum Aminotransferases

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with enoxaparin sodium. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

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

Local Reactions

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

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

Other adverse reactions that were thought to be possibly or probably related to treatment with enoxaparin sodium, heparin, or placebo in clinical studies with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the enoxaparin sodium group, are provided below (see Tables below).

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

Adverse Reaction	**Dosing Regimen**			
	~~Enoxaparin sodium~~ 40 mg daily subcutaneously		**Heparin** 5000 U q8h subcutaneously	
	n=1228 %		n=1234 %	
	Severe	**Total**	**Severe**	**Total**
Hemorrhage	<1	7	<1	6
Anemia	<1	3	<1	3
Ecchymosis	0	3	0	3

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

Adverse Reaction	**Dosing Regimen**									
	Enoxaparin sodium 40 mg daily subcutaneously				**Enoxaparin sodium** 30 mg q12h subcutaneously n=1080 %		**Heparin** 15,000 U/24h subcutaneously n=766 %		**Placebo** q12h subcutaneously n=115 %	
	Peri-operative Period n=288* %		Extended Prophylaxis Period n=131† %							
	Severe	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Fever	0	8	0	0	<1	5	<1	4	0	3
Hemorrhage	<1	13	0	5	<1	4	1	4	0	3
Nausea					<1	3	<1	2	0	2
Anemia	0	16	0	<2	<1	2	2	5	<1	7
Edema					<1	2	<1	2	0	2
Peripheral edema	0	6	0	0	<1	3	<1	4	0	3

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

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

Table 10: Adverse Reactions Occurring at ≥2% Incidence in Enoxaparin Sodium-Treated Medical Patients with Severely Restricted Mobility During Acute Illness

Adverse Reaction	**Dosing Regimen**	
	~~Enoxaparin sodium~~ 40 mg daily subcutaneously n=360 %	**Placebo** daily subcutaneously n=362 %
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7

Nausea	2.5	1.7

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

Adverse Reaction	**Dosing Regimen**					
	Enoxaparin sodium 1.5 mg/kg daily subcutaneously n=298 %		**Enoxaparin sodium** 1 mg/kg q12h subcutaneously n=559 %		**Heparin** aPTT Adjusted Intravenous Therapy n=544 %	
	Severe	**Total**	**Severe**	**Total**	**Severe**	**Total**
Injection Site Hemorrhage	0	5	0	3	<1	<1
Injection Site Pain	0	2	0	2	0	0
Hematuria	0	2	0	<1	<1	2

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

Non-hemorrhagic clinical events reported to be related to Enoxaparin Sodium therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic events, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with subcutaneous enoxaparin Sodium than in patients treated with intravenous heparin.

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

Table 12: Serious Adverse Events Occurring at ≥0.5% Incidence in enoxaparin sodiumtreated patients with Unstable Angina or Non–Q-Wave Myocardial Infarction

Adverse Event	**Dosing Regimen**	
	Enoxaparin sodium 1 mg/kg q12h subcutaneously n=1578 n (%)	**Heparin** aPTT Adjusted Intravenous Therapy n=1529 n (%)
Atrial fibrillation	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)

Adverse Reactions in enoxaparin sodium-Treated Patients with Acute ST-Segment Elevation Myocardial Infarction

In a clinical study in patients with acute ST-segment elevation myocardial infarction, thrombocytopenia occurred at a rate of 1.5%.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of enoxaparin sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of 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 indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis.
Local reactions at the injection site (e.g. nodules, inflammation, oozing), systemic allergic reactions (e.g. pruritus, urticaria, anaphylactic/anaphylactoid reactions including shock), vesiculobullous rash, cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thrombocytopenia with thrombosis (see Section 4.4) 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 have been reported
Osteoporosis has also been reported following long-term therapy.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacodynamics
In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean ±SD, 14.0±3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean ±SD, 1.22±0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose (100 mg/mL

concentration), administered subcutaneously every 12 hours to patients in a large clinical study resulted in aPTT values of 45 seconds or less in the majority of patients (n=1607). A 30 mg intravenous bolus immediately followed by a 1 mg/kg subcutaneous administration resulted in aPTT postinjection values of 50 seconds. The average aPTT prolongation value on Day 1 was about 16% higher than on Day 4.

Clinical studies:

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

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

In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Asian and 0.4% others. Enoxaparin sodium 40 mg subcutaneously, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5000 U every 8 hours subcutaneously in reducing the risk of DVT. The efficacy data are provided below (see Table 13).

Table 13: Efficacy of enoxaparin sodium in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	**Dosing Regimen**	
	Enoxaparin sodium 40 mg daily subcutaneously n (%)	**Heparin** 5000 U q8h subcutaneously n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures Total VTE* (%)	56 (10.1) (95% CI†: 8 to 13)	63 (11.3) (95% CI: 9 to 14)
DVT Only (%)	54 (9.7) (95% CI: 7 to 12)	61 (10.9) (95% CI: 8 to 13)

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

† CI = Confidence Interval

In a second double-blind, parallel group study, enoxaparin sodium 40 mg subcutaneously once a day was compared to heparin 5000 U every 8 hours subcutaneously in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below (see Table 14).

Table 14: Efficacy of enoxaparin sodium in the Prophylaxis of Deep Vein Thrombosis Following Colorectal Surgery

Indication	**Dosing Regimen**	
	Enoxaparin sodium 40 mg daily subcutaneously n (%)	**Heparin** 5000 U q8h subcutaneously n (%)

All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures Total VTE* (%)	48 (7.1) (95% CI†: 5 to 9)	45 (6.7) (95% CI: 5 to 9)
DVT Only (%)	47 (7.0) (95% CI: 5 to 9)	44 (6.5) (95% CI: 5 to 8)

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
Enoxaparin sodium has been shown to reduce the risk of postoperative deep vein thrombosis (DVT) following hip or knee replacement surgery.

In a double-blind study, enoxaparin sodium 30 mg every 12 hours subcutaneously was compared to placebo in patients with hip replacement. A total of 100 patients were randomized in the study and all patients were treated. Patients ranged in age from 41 to 84 years (mean age 67.1 years) with 45% men and 55% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued for 10 to 14 days after surgery. The efficacy data are provided below (see Table 15).

Table 15: Efficacy of enoxaparin sodium in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

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

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

A double-blind, multicenter study compared three dosing regimens of enoxaparin sodium in patients with hip replacement. A total of 572 patients were randomized in the study and 568 patients were treated. Patients ranged in age from 31 to 88 years (mean age 64.7 years) with 63% men and 37% women. Patients were 93% Caucasian, 6% Black, <1% Asian, and 1% others. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The efficacy data are provided below (see Table 16).

Table 16: Efficacy of enoxaparin sodium in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

	Dosing Regimen		
Indication	**10 mg daily subcutaneously** n (%)	**30 mg q12h subcutaneously** n (%)	**40 mg daily subcutaneously** n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)
Treatment Failures Total DVT (%)	40 (25)	22 (11) *	27 (14)

Proximal DVT (%)	17 (11)	8 (4) †	9 (5)

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

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

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimen. 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 17).

Table 17: Efficacy of enoxaparin sodium in the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery.

Indication	**Dosing Regimen**	
	Enoxaparin sodium 30 mg q12h subcutaneously n (%)	**Placebo** q12h subcutaneously n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures Total DVT (%)	5 (11) * (95% CI†: 1 to 21)	32 (62) (95% CI: 47 to 76)
Proximal DVT (%)	0 (0) ‡ (95% Upper CL§: 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 hours subcutaneously in patients undergoing elective knee replacement surgery was compared to heparin 5000 U every 8 hours subcutaneously. A total of 453 patients were randomized in the study and all were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, and 0.6% others. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was lower for enoxaparin sodium compared to heparin.

Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin sodium 40 mg subcutaneously, initiated up to 12 hours prior to surgery for the prophylaxis of postoperative DVT. At the end of the peri-operative period, all patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin sodium 40 mg (n=90) once a day subcutaneously or to placebo (n=89) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 69.4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo. The efficacy data are provided below (see Table 18).

Table 18: Efficacy of Enoxaparin sodium in the Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

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

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 [21%]; p=<0.001).

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 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 19).

Table 19: Efficacy of Enoxaparin sodium in the Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	**Dosing Regimen**		
	~~**Enoxaparin sodium**~~ 20 mg daily subcutaneously n (%)	~~**Enoxaparin sodium**~~ 40 mg daily	**Placebo** n (%)

		subcutaneously n (%)	
All Treated Medical Patients During Acute Illness	351 (100)	360 (100)	362 (100)
Treatment Failure*	43 (12.3)	16 (4.4)	43 (11.9)
Total VTE† (%)	43 (12.3) (95% CI‡ 8.8 to 15.7)	16 (4.4) (95% CI‡ 2.3 to 6.6)	41 (11.3) (95% CI‡ 8.1 to 14.6)
Total DVT (%)			
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 in origin

‡ 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.

Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

In a multicenter, parallel group study, 900 patients with acute lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) enoxaparin sodium 1.5 mg/kg once a day subcutaneously, (ii) enoxaparin sodium 1 mg/kg every 12 hours subcutaneously, or (iii) heparin intravenous bolus (5000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 60.7 years) with 54.7% men and 45.3% women. All patients also received warfarin sodium (dose adjusted according to PT to achieve an International Normalization Ratio [INR] of 2.0 to 3.0), commencing within 72 hours of initiation of enoxaparin sodium or standard heparin therapy, and continuing for 90 days. enoxaparin sodium or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both enoxaparin sodium regimens were equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism (DVT and/or PE). The efficacy data are provided below (see Table 20).

Table 20: Efficacy of Enoxaparin sodium in Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

Indication	**Dosing Regimen***		
	~~**Enoxaparin sodium**~~ 1.5 mg/kg daily subcutaneously n (%)	**Enoxaparin sodium** 1 mg/kg q12h subcutaneously n (%)	**Heparin** aPTT Adjusted Intravenous Therapy n (%)
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Patient Outcome Total VTE† (%)	13 (4.4) ‡	9 (2.9) ‡	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 outpatient heparin therapy because of associated comorbid conditions or potential for non-compliance and inability to attend follow-up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but ONLY enoxaparin sodium patients were permitted to go home on therapy (72%). A total of 501 patients were randomized in the study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8 years) with 60.5% men and 39.5% women. Patients were randomized to either enoxaparin sodium 1 mg/kg every 12 hours subcutaneously or heparin intravenous bolus (5000 IU) followed by a continuous infusion administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also received warfarin sodium as described in the previous study. Enoxaparin sodium or standard heparin therapy was administered for a minimum of 5 days. Enoxaparin sodium was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are provided below (see Table 21).

Table 21: Efficacy of Enoxaparin sodium in Treatment of Deep Vein Thrombosis

Indication	**Dosing Regimen***	
	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† (%)	13 (5.3) ‡	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	**2** (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).

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

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

therapy at 14 days after initiation of treatment. The lower incidence of the triple endpoint was sustained up to 30 days after initiation of treatment. These results were observed in an analysis of both all-randomized and all-treated patients. The efficacy data are provided below (see Table 22).

Table 22: 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).

Indication	**Dosing Regimen***			
	~~Enoxaparin sodium~~ 1 mg/kg q12h subcutaneous n (%)	**Heparin** aPTT Adjusted Intravenous Therapy n (%)	**Reduction** (%)	**p Value**
All Treated Unstable Angina and Non–Q-Wave MI Patients	1578 (100)	1529 (100)		
Time point† 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

***** 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).

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 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 or myocardial infarction)

Indication	**Dosing Regimen***			
	~~Enoxaparin sodium~~ 1 mg/kg q12h	**Heparin** aPTT Adjusted Intravenous	**Reduction** (%)	**p Value**
	subcutaneously n (%)	Therapy n (%)		
All Treated Unstable Angina and Non–Q-Wave MI Patients	1578 (100)	1529 (100)		
Time point† 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

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

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

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 heparin.

Study medication was initiated between 15 minutes before and 30 minutes after the initiation of fibrinolytic therapy. Unfractionated heparin was administered beginning with an intravenous bolus of 60 U/kg (maximum 4000 U) and followed with an infusion of 12 U/kg per hour (initial maximum 1000 U per hour) that was adjusted to maintain an aPTT of 1.5 to 2 times the control value. The intravenous 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 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 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.

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.

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

The rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, and 12.0% in the unfractionated heparin group, a 17% reduction in the relative risk, (P=0.000003) (see Table 24).

Table 24: Efficacy of Enoxaparin sodium in the Treatment of Acute ST-Segment Elevation Myocardial Infarction

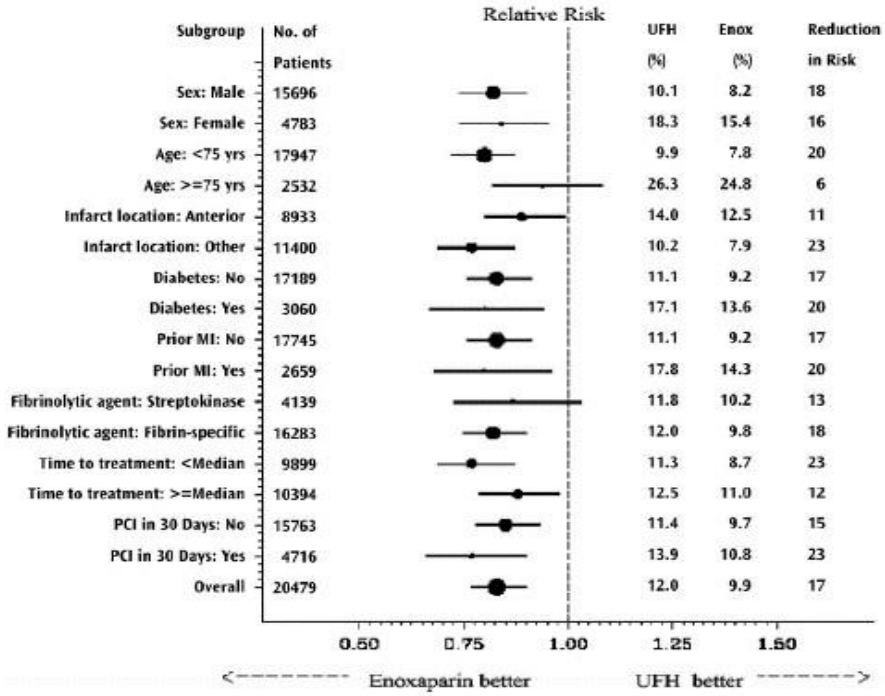
	Enoxaparin (N=10,256)	**UFH (N=10,223)**	**Relative Risk (95% CI)**	**P Value**
Outcome at 48 hours	n (%)	n (%)		

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	213 (2.1)	286 (2.8)	0.74 (0.62 to 0.88)	<0.001
Re-infarction or				
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. CI denotes confidence intervals.

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 administered, and time to treatment with study drug (see Figure 1); however, it is necessary to interpret such subgroup analyses with caution.

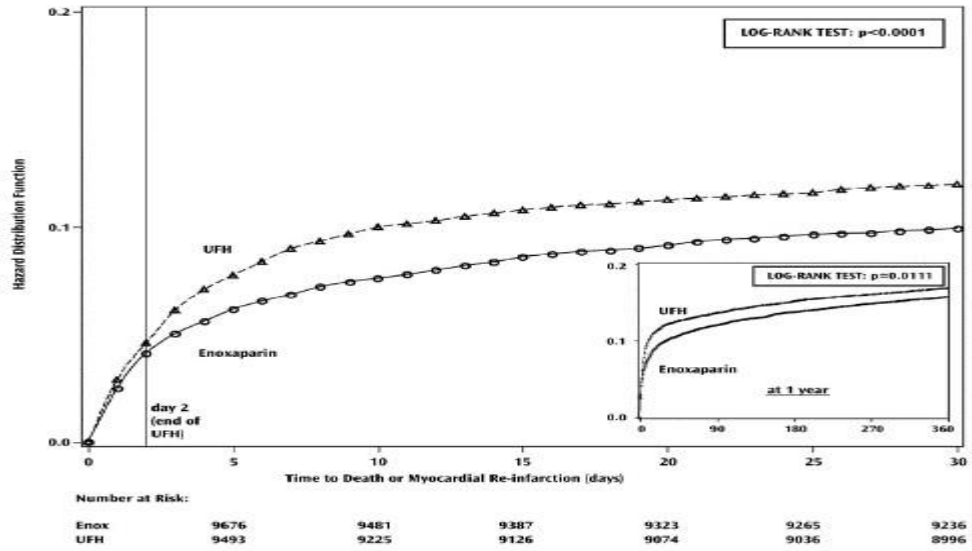
Figure 1: Relative Risks of and Absolute Event Rates for the Primary Endpoint at 30 Days in Various Subgroups*



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

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

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

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 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 significantly lower in the enoxaparin group (10.1%) as compared to the heparin group (12.2%).

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetic studies were conducted using the 100 mg/mL formulation. Maximum antiFactor 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 a 1 mg/kg subcutaneously every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 84% of steady-state levels. Steady state is achieved on the second day of treatment.

Enoxaparin pharmacokinetics appears to be linear over the recommended dosage ranges (see section 4.2) After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg oncedaily 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 25).

Table 25: Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg subcutaneously Once-Daily Doses of Enoxaparin Sodium Using 100 mg/mL or 200 mg/mL Concentrations.

	Concentration	**Anti-Xa**	**Anti-IIa**	**Heptest**	**aPTT**
Amax (IU/mL or Δ sec)	100 mg/mL	1.37 (±0.23)	0.23 (±0.05)	105 (±17)	19 (±5)
	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	111 (±17)	22 (±7)
	90% CI	102%-110%		102%-111%	
† **tmax** (h)	100 mg/mL	3 (2-6)	4 (2-5)	2.5 (2-4.5)	3 (2-4.5)
	200 mg/mL	3.5 (2-6)	4.5 (2.5-6)	3.3 (2-5)	3 (2-5)
AUC (ss) (h*IU/mL or h* Δ sec)	100 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)	
	200 mg/mL	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)	
	90% CI	105%-112%		103%-109%	

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

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

Elimination
Following intravenous dosing, the total body clearance of enoxaparin is 26 mL/min. After intravenous dosing of enoxaparin labeled with the gamma-emitter, ^{99m}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 SC dose to about 7 hours after repeated dosing. Significant anti-Factor Xa activity persists in plasma for about 12 hours following a 40 mg 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 A_{max} derived from anti-Factor Xa values following single subcutaneous dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters has not been conclusively identified; however, body weight may be a contributing factor.

Weight

After repeated subcutaneous 1.5 mg/kg once-daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while A_{max} is not increased.
When non–weight-adjusted dosing was administered, it was found after a single-subcutaneous 40 mg dose, that anti-Factor Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects.

Geriatric
Apparent clearance and A_{max} derived from anti-Factor Xa values following single and multiple subcutaneous dosing in geriatric subjects were close to those observed in young subjects.
Following once a day subcutaneous dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value (see section 4.2).

Renal Impairment
A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady state, is marginally increased in mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-50 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 section 4.2).

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

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

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

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical studies was 2.0 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^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.

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/m^2/day and 410 mg/m^2/day in rats and rabbits respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide
Water for Injection

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the Active Ingredients.

6.3 Shelf life 24
Months

6.4 Special precautions for storage Store
below 30°C. Do not freeze.

6.5 Nature and contents of container

A blister containing 1 ml pre filled glass syringe and a leaflet packed in a carton.

6.6 Special precautions for disposal and other handling

Immediately dispose of the syringe in the nearest sharp container. Keep out of the reach of children.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

FDA/SD.173-121168

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/4/2017

10. DATE OF REVISION OF THE TEXT

07/2025