

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Over 2800 patients, 65 years and older, have received enoxaparin sodium in clinical trials. The efficacy of enoxaparin sodium in the geriatric (>65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of enoxaparin sodium were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when enoxaparin sodium was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of enoxaparin sodium-associated bleeding increased with age. Serious adverse events increased with age for patients receiving enoxaparin sodium. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin sodium between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Enoxaparin sodium should be used with care in geriatric patients who may show delayed elimination. The incidence 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=1051). Patients >75 years of age did not receive a 30 mg intravenous bolus prior to the normal dosage regimen and had their subcutaneous dose adjusted to 0.75 mg/kg every 12 hours [see *Dosage and Administration* (2.4)]. The incidence of bleeding complications was higher in patients >65 years of age as compared to younger patients (<65 years).

8.6 Patients with Mechanical Prosthetic Heart Valves

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

8.7 Renal Impairment

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

8.8 Low-Weight Patients

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

8.9 Obese Patients

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

10 OVERDOSAGE

Accidental 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 reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

11 DESCRIPTION

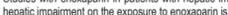
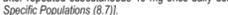
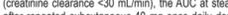
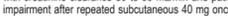
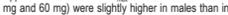
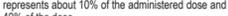
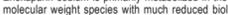
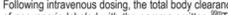
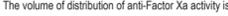
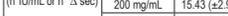
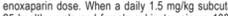
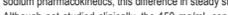
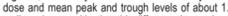
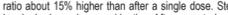
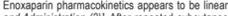
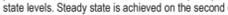
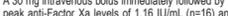
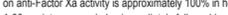
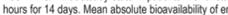
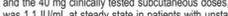
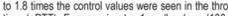
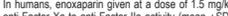
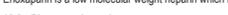
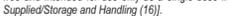
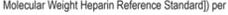
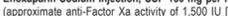
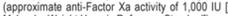
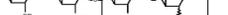
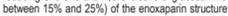
Enoxaparin Sodium Injection, USP is an aqueous solution containing enoxaparin sodium, a low molecular weight heparin. The pH of the injection is 5.5 to 7.5. Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-epinepranoic 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:

<2,000 daltons <20%

2,000 to 8,000 daltons >60%

>8,000 daltons <18%

STRUCTURAL FORMULA



Weight

After repeated subcutaneous 1.5 mg/kg once-daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30 to 48 kg/m²) compared to non-obese control subjects, while A_∞ is not increased.

When non-weight-adjusted dosage 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* (8.6)].

Pharmacokinetic Interaction

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous dosages of 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 m²).

13.2 Animal Toxicology and/or Pharmacology

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

13.3 Reproductive and Developmental Toxicology

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

14 CLINICAL STUDIES

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

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

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

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

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

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

† CI = Confidence Interval

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

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

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

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

† CI = Confidence Interval

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

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

In a double-blind study, enoxaparin sodium 30 mg every 12 hours subcutaneously was compared to placebo in patients with hip replacement. A total of 100 patients were randomized in the study and all patients were treated. Patients ranged in age from 41 to 84 years (mean age 57.1 years) with 45% men and 55% women.