Clotinex®

Enoxaparin Sodium BP

PRESENTATION
Clotinex® 40: Each pre-filled syringe (0.4 ml) contains Enoxaparin Sodium BP 40 mg equivalent to 4000 anti-Xa IU.
Clotinex® 60: Each pre-filled syringe (0.6 ml) contains Enoxaparin Sodium BP 60 mg equivalent to 6000 anti-Xa IU.

PHARMACEUTICAL FORM
Clotinex 40 Injection is a sterile solution of Enoxaparin Sodium in water for injection filled in graduated syringe with needle shield and black plunger stopper. It is clear colorless transparent solution. Free from any visible foreign particles.

DESCRIPTION
Enoxaparin Sodium is a low molecular weight heparin with a high anti-Xa activity and low anti-IIa or antithrombin activity. At doses required for the various indications, Enoxaparin Sodium does not increase bleeding time. At preventive doses, Enoxaparin Sodium causes no notable modification of activated Partial Thromboplastin Time (aPTT). It neither influences platelet aggregation nor binding of fibrinogen to platelets. Enoxaparin Sodium is primarily metabolised in the liver.

INDICATIONS & USES
- Treatment of deep vein thrombosis, with or without pulmonary embolism
- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin
- Prevention of thrombus formation in extra corporeal circulation during hemodialysis
- Prophylaxis of venous thromboembolic disease (prevention of blood clot formation in the veins), in particular those which may be associated with orthopaedic or general surgery
- Prophylaxis of venous thromboembolic disease in medical patients bedridden due to acute illnesses, including cardiac insufficiency, respiratory failure, severe infections, rheumatic diseases

PHARMACOLOGY
Pharmacodynamic properties
Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa.
Enoxaparin sodium is characterised by a higher ratio of antithrombotic activity to anticoagulant activity than unfractionated heparin. At recommended doses, it does not significantly influence platelet aggregation, binding of fibrinogen to platelets or global blood clotting tests such as APTT and prothrombin time.
Enoxaparin binds to anti-thrombin III leading to inhibition of coagulation factors IIa and Xa. Enoxaparin has been shown to increase the blood concentration of Tissue Factor Pathway Inhibitor in healthy volunteers.

Pharmacokinetic properties
Enoxaparin is rapidly and completely absorbed following subcutaneous injection. The maximum plasma anti-Xa activity occurs 1 to 4 hours after injection with peak activities in the order of 0.16 IU/ml and 0.38 IU/ml after doses of 20 mg or 40 mg respectively.
The anti-Xa activity generated is localised within the vascular compartments and elimination is characterised by a half-life of 4 to 5 hours. Following a 40 mg dose, anti-Xa activity may persist in the plasma for 24 hours.
A 30mg IV bolus immediately followed by a 1mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1.16IU/ml (n=16) and average exposure corresponding to 88% of steady state levels.
A linear relationship between anti-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. In patients with severe renal impairment (creatinine clearance < 30 ml/min), the AUC at steady state is significantly increased by an average of 65% after repeated, once daily subcutaneous doses of 40mg.
Hepatic metabolism by desulphation and depolymerisation also contributes to elimination. The elimination half-life may be prolonged in elderly patients although no dosage adjustment is necessary.
A study of repeated, once daily subcutaneous doses of 1.5 mg/kg in healthy volunteers suggests that no dosage adjustment is necessary in obese subjects (BMI 30-48 kg/m2) compared to non-obese subjects. Enoxaparin, as detected by anti-Xa activity, does not cross the placental barrier during the second trimester of pregnancy.
Low Body Weight
When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 40 mg dose, that anti-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.

Indications	Recommended Dosage Schedule
Treatment of deep vein thrombosis, with or without pulmonary embolism	Subcutaneously 100 anti-Xa IU/kg twice daily for 10 days or Subcutaneously 150 anti-Xa IU/kg once daily for 10 days
	Oral anticoagulant therapy should be initiated when appropriate and Enoxaparin Sodium treatment should be continued until a therapeutic anticoagulant effect has been achieved.
Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin	Subcutaneously 100 anti-Xa IU/kg twice daily for 2 - 8 days
	Should be administered concurrently with oral aspirin (100 to 325 mg once daily). Treatment with Enoxaparin Sodium in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilization.
Prevention of thrombus formation in extra corporeal circulation during hemodialysis	Recommended dose is 100 anti-Xa IU/kg For patients with a high risk of hemorrhage, the dose should be reduced to 50 anti-Xa IU/kg for double vascular access or 75 anti-Xa IU/kg for single vascular access.
	During hemodialysis, Enoxaparin Sodium should be introduced into the arterial line of the circuit at the beginning of the dialysis session
Prophylaxis of venous thromboembolic disease in surgical patients	Patients undergoing general surgery with a moderate risk of thromboembolism (e.g. abdominal surgery): Subcutaneously 2000 anti-Xa IU (0.2 ml) or 4000 anti-Xa IU (0.4 ml) once daily for 7 to 10 days. The first injection should be given 2 hours before the surgical procedure. Patients undergoing orthopedic surgery with a high risk of thromboembolism: Subcutaneously 4000 anti-Xa IU (0.4 ml) once daily for 7 to 10 days. The first injection should be given 12 hours before the surgical procedure.
	Longer treatment duration may be appropriate in some patients like continued therapy with 4000 anti-Xa IU once daily for 3 weeks following the initial therapy has been proven to be beneficial in orthopaedic surgery.
Prophylaxis of venous thromboembolic disease in medical patients	Subcutaneously 4000 anti-Xa IU (0.4 ml) once daily for 6 - 14 days

Dose in Elderly Patients:
No dosage adjustment is necessary, unless kidney function is impaired.

Dose in Renal Impairment:
Although no dosage adjustment is recommended in patients with moderate (creatinine clearance: 30-50 ml/min) and mild (creatinine clearance: 50-80 ml/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding. For patients with severe (creatinine clearance <30 ml/min) renal impairment, following dosage adjustments are recommended: Prophylactic dose ranges: 2000 anti-Xa IU once daily; Therapeutic dose ranges: 100 anti-Xa IU/kg once daily.

Dose in Hepatic Impairment:
Caution should be used in hepatically impaired patients.

CONTRAINDICATION
Patients with known hypersensitivity to Enoxaparin Sodium, heparin or other low molecular weight heparins. Patients with active major bleeding and conditions with a high risk of uncontrolled hemorrhage including recent hemorrhagic stroke.

SIDE EFFECTS
Hemorrhage (bleeding), thrombocytopenia, elevations of serum amino transferase, pain, bluish marks at injection site, skin rash at injection site, cases of neuraxial hematomas with concurrent use of Enoxaparin and spinal/epidural anesthesia or spinal puncture have resulted in varying degrees of neurological injuries.

PRECAUTION
Enoxaparin Sodium should be injected by deep subcutaneous route in prophylactic and curative treatment and by intravascular route during hemodialysis. Do not administer by the intramuscular route. Enoxaparin Sodium should be used with caution in conditions with increased potential for bleeding, such as impaired hemostasis, history of peptic ulcer, recent ischemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy and recent neuro- or ophthalmologic surgery, concomitant use of medications affecting hemostasis. It is recommended that the platelet counts be measured before the initiation of the treatment and regularly thereafter during treatment.

USE IN PREGNANCY AND LACTATION
Pregnancy:
Pregnancy category B. In humans, there is no evidence that Enoxaparin Sodium crosses the placental barrier. As there are no adequate and well-controlled studies in pregnant women, Enoxaparin Sodium should be used during pregnancy only if clearly needed. Pregnant women with mechanical prosthetic heart valves may be at a higher risk for thromboembolism.

Nursing mothers:
It is not known whether Enoxaparin 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, a decision should be made whether to discontinue nursing or discontinue Enoxaparin, taking into account the importance of Enoxaparin to the mother and the known benefits of nursing.

USE IN CHILDREN
Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTION
It is recommended that agents which affect hemostasis should be discontinued prior to Enoxaparin Sodium therapy unless strictly indicated. These agents include medications such as: acetylsalicylic acid (and derivatives), NSAIDs (including ketorolac), ticlopidine, clopidogrel, dextran 40, glucocorticoids, thrombolytics and anticoagulants, other antiplatelet aggregation agents including glycoprotein IIb/IIIa antagonists. If the combination is indicated, should be used with careful clinical and laboratory monitoring.

OVERDOSE
Accidental overdosage may lead to bleeding complications. Injected Enoxaparin may be largely neutralized by the slow IV injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Enoxaparin injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Enoxaparin.

STORAGE CONDITION
Do not store above 30°C. Do not store in a refrigerator or freezer.
Keep out of the reach of children.

HOW SUPPLIED
Clotinex® 40: Each box contains 1 pre-filled syringe containing 40 mg (4000 anti-Xa IU/0.4 ml) Enoxaparin Sodium BP in alu-alu blister pack.
Clotinex ® 60: Each box contains 1 pre-filled syringe containing 60 mg (6000 anti-Xa IU/0.6 ml) Enoxaparin Sodium BP in alu-alu blister pack.

SQUARE