

Low Molecular weight Heparin

Enoxaparin Sodium Injection BP

Composition : Each 0.4 ml pre-filled Syringe Contains :

Enoxaparin Sodium BP 40 mg (4000 IU)
Water for injections BP q.s to 0.4 ml

Indications

Enoxaparin injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

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.

Enoxaparin injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave

myocardial infarction, when concurrently administered with aspirin.

Enoxaparin 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.

Mechanism of Action

Enoxaparin binds to and accelerates the activity of antithrombin III. By activating antithrombin III, enoxaparin preferentially potentiates the inhibition of coagulation factors V and X. The anticoagulant effect of enoxaparin can be directly correlated to its ability to inhibit factor Xa. Factor Xa catalyzes the conversion of prothrombin to thrombin, so enoxaparin's inhibition of this process results in decreased thrombin and ultimately the prevention of fibrin clot formation.

Pharmacokinetic

Absorption

Bioavailability

Mean absolute bioavailability of 92% when given sub-Q (based on anti-Factor Xa activity).

Onset

Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3–5 hours after administration.

Duration

Substantial anti-Factor Xa activity persists in plasma for about 12 hours following administration (40 mg once daily).

Protein binding

80% bound-albumin

Metabolism

Undergoes desulfation and polymerization via the liver

Distribution

Excretion

About 6 L (based on anti-Factor Xa activity).

Not known whether enoxaparin is distributed into milk.

Does not appear to cross placenta.

Elimination

Thrombolytic Role

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.

Half-life

4.5 hours (based on anti-Factor Xa activity).

Contraindications

The use of Enoxaparin Sodium injection BP should be avoided in the following cases:

Hypersensitivity to either enoxaparin sodium, heparin or its derivatives including other Low

Molecular Weight Heparins;

Active bleeding or serious blood coagulation disorder;

History or presence of thrombocytopenia following administration of enoxaparin or other heparin

through a type II immunologic mechanism

Active gastrointestinal ulcer;

Cerebrovascular episodes (unless there are systemic emboliisms).

Acute bacterial endocarditis.

Adverse Effects

Haemorrhage

During enoxaparin sodium therapy, bleeding may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the use of medications affecting haemostasis

The origin of the bleeding should be investigated and appropriate treatment instituted. Major haemorrhage including retroperitoneal and intracranial bleeding has been reported. Some of these cases have been lethal. There have been reports of neuronal haematomas with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture. These events have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis.

Thrombocytopenia

Mild, transient, asymptomatic thrombocytopenia (type I) has been reported during the first days of therapy. Rare cases of immuno-allergic thrombocytopenia with or without thrombosis have been reported.

Local reactions

Pain, hematoma, and mild local irritation may follow the subcutaneous injection of enoxaparin sodium. Rarely, hard inflammatory nodules, which are not cystic enclosures of enoxaparin sodium, have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation. Exceptional cases of skin necrosis at the injection site have been reported with heparins and Low Molecular Weight Heparins. These phenomena are usually preceded by purpura or erythematous plaques, infiltrated and painful. Treatment must be discontinued.

Others

Very rare cases of hypersensitivity cutaneous vasculitis have been reported.

Warnings and Precautions

Warnings

Neurologic Effects

Epidural or spinal hematomas and neurologic injury, including long-term or permanent paralysis, associated with concurrent use of low molecular weight heparins and neuraxial (spinal/epidural) anesthesia or spinal puncture procedures. Frequent monitoring for signs of neurologic impairment recommended.

Hematologic Effects

Use with extreme caution in patients with an increased risk of hemorrhage. Such patients include those with bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic GI disease, hemorrhagic stroke, or recent brain, spinal, or ophthalmologic surgery. Increased risk for hemorrhage in patients treated concomitantly with platelet inhibitors.

Carefully monitor patients with low body weight or renal impairment for signs and symptoms of bleeding. As with other anticoagulants, bleeding may occur at any site during therapy. Major (sometimes fatal) hemorrhages, including retroperitoneal and intracranial bleeding, have been reported. Search for bleeding site if an unexplained fall in hematocrit or blood pressure occurs. If enoxaparin overdose occurs, protamine sulfate may be administered. Because fatal reactions resembling anaphylaxis have been reported with protamine sulfate administration, use only when resuscitation techniques and treatment for anaphylactic shock are readily available.

Valve thrombosis that was potentially fatal and/or required surgical intervention reported during prophylaxis in some patients (including pregnant women) with mechanical prosthetic heart valves. Women with mechanical prosthetic heart valves are at higher risk for thromboembolism during pregnancy. If enoxaparin is used, monitor anti-factor Xa concentrations frequently and adjust dosage appropriately to maintain anti-factor Xa concentrations at approximately 1–1.2 units/mL.

Precautions Hematologic Effects

Periodic CBCs, including platelet counts, and stool occult blood tests are recommended. If abnormal coagulation parameters or bleeding

should occur, monitor anti-factor Xa levels.

If thromboembolic events occur despite prophylaxis, institute appropriate therapy.

Pregnancy and Lactation

Pregnancy

Animal studies have not shown any evidence of foetotoxicity or teratogenicity. In the pregnant rat, the transfer of ³⁵S-enoxaparin across the maternal placenta to the foetus is minimal.

In humans, there is no evidence that enoxaparin crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the first and the third trimesters.

As there are no adequately powered and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need.

Pregnant women with mechanical prosthetic heart valves

The use of enoxaparin 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 bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal death. There have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism.

Enoxaparin sodium is not recommended for use in pregnant women with prosthetic heart valves (see section 4.4 Special warnings and precautions for use: Prosthetic heart valves).

Lactation

In lactating rats, the concentration of ³⁵S-enoxaparin or its labelled metabolites in milk is very low.

It is not known whether unchanged enoxaparin is excreted in human breast milk. The oral absorption of enoxaparin is unlikely. However, as a precaution, lactating mothers receiving enoxaparin should be advised to avoid breast-feeding.

Interactions

It is recommended that agents which affect haemostasis should be discontinued prior to enoxaparin therapy unless their use is essential, such as: systemic salicylates, acetylsalicylic acid, NSAIDs including ketorolac, dextran, and clopidogrel, systemic glucocorticoids, thrombolytics and anticoagulants. If the combination cannot be avoided, enoxaparin should be used with careful clinical and laboratory monitoring.

Dosage and Administration

Prophylaxis of deep vein thrombosis

In patients with a moderate risk of thromboembolism (e.g. abdominal surgery), the recommended dose of enoxaparin sodium is 2000 anti-Xa IU (20 mg) or 4000 anti-Xa IU (40 mg) or 6000 anti-Xa IU (60 mg) once daily by subcutaneous injection. In general surgery, the first injection should be given 2 hours before the surgical procedure.

In patients with a high risk of thromboembolism (e.g. orthopedic surgery), the recommended dose of enoxaparin sodium given by subcutaneous injection, is 4000 anti-Xa IU (40 mg) once daily, initiated 12 hours prior to surgery or 3000 anti-Xa IU (30 mg) twice daily, initiated 12 to 24 hours after surgery. Enoxaparin sodium treatment should be prescribed for as long as there is a risk of thromboembolism, usually until the patient is discharged from the clinic or hospital (an average period of 7 to 10 days after the surgery). Continued therapy with 4000 anti-Xa IU (40 mg) once daily for 3 weeks following the initial therapy has been proven to be beneficial in orthopedic surgery. Under normal conditions

of use, enoxaparin sodium does not alter the general blood coagulation tests and therefore, it is pointless to monitor the progress of the treatment with these tests. For special recommendations concerning dosing intervals for "spinal/epidural anaesthesia" and "percutaneous coronary revascularisation procedures"

Prophylaxis of venous thromboembolism in medical (non surgical) patients The recommended dose of enoxaparin sodium is 2000 anti-Xa IU (20 mg) or 4000 anti-Xa IU (40 mg) or 6000 anti-Xa IU (60 mg) once daily by subcutaneous injection. Treatment with enoxaparin sodium is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days.

Treatment of deep vein thrombosis with or without pulmonary embolism

For the treatment of deep vein thrombosis with or without pulmonary embolism, 100 anti-Xa IU/kg (1 mg/kg) of body weight of enoxaparin sodium are administered twice daily (every 12 hours), subcutaneously. In patients with no thromboembolic risk followed also by no symptoms of pulmonary embolism 150 anti-Xa IU/kg (1.5 mg/kg) Enoxaparin Sodium injection BP should be given once daily. Enoxaparin sodium treatment is usually prescribed for an average period of 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 (International Normalisation Ratio 2 to 3).

Treatment of unstable angina and non-Q-wave myocardial infarction

The recommended dose of enoxaparin sodium is 100 anti-Xa IU/kg (1 mg/kg) every 12 hours by subcutaneous injection, 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.

The usual duration of treatment is 2 to 8 days.

Prevention of extra corporeal thrombus during haemodialysis

In patients who undergo repeated sessions of haemodialysis, the prevention of thrombosis is the extra corporeal circulation during haemodialysis is achieved by the administration of one dose of 100 anti-Xa IU/kg (1 mg/kg) into the arterial line of the circuit of the haemodialysis at the beginning of the session.

The effect of this dose is usually sufficient for a 4-hour session of haemodialysis; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 50 to 100 anti-Xa IU/kg (0.5 to 1 mg/kg) may be given. For patients with a high risk of haemorrhage, the recommended dose should be reduced to 50 anti-Xa IU/kg (0.5 mg/kg) (for double vascular access) or 75 anti-Xa IU/kg (0.75 mg/kg) (for single vascular access).

Method of administration

The pre-filled disposable syringe is ready for immediate use. Enoxaparin Sodium is administered by deep subcutaneous injection.

The administration should be alternated between the left and right anterolateral or posterolateral abdominal wall. The whole length of the needle should be introduced vertically into a skin fold gently held between the thumb and index finger. The skin fold should not be released until the injection is complete. Do not rub the injection site after administration.

When using ampoules or vials of enoxaparin sodium, the volume to be injected should be measured precisely with a graduated syringe fitted with an appropriate needle for subcutaneous injection.

Symptoms and treatment of Overdose

If enoxaparin overdose occurs, protamine sulfate may be administered. Because fatal reactions resembling anaphylaxis have been reported with protamine sulfate administration, use only when resuscitation techniques and treatment for anaphylactic shock are readily available.

If a thromboembolic event occurs despite enoxaparin prophylaxis, discontinue the drug and initiate appropriate therapy. Cases of heparin-induced thrombocytopenia with thrombosis reported, including complications such as organ infarction, limb ischemia, or death.

Use with extreme caution in patients with a history of heparin-induced thrombocytopenia. Monitor thrombocytopenia of any degree closely.

If platelet count falls to <100,000/mm³, discontinue therapy.]

Presentation

Enoxaparin Sodium Injection BP (40 mg/0.4 ml):

Box that contains 2 pre-filled syringes of 0.4 ml in blister packaging

Shelf Life : 24 months

Storage : Store below 25 °C. Do not allow to freeze.

Marketed by:



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