enoxaparin sodium

**Presentations and forms**
Subcutaneous and intravascular injectable solution of 20 mg/0.2 ml and 40 mg/0.4 ml:
Pre-filled syringes, box of 2.
Subcutaneous injectable solution of 60 mg/0.6 ml, 80 mg/0.8 ml or 100 mg/1 ml:
Pre-filled syringes, box of 10.

**Indications**
Injectable solution of 20 mg and 40 mg:
- Prophylaxis of venous thromboembolic disease in moderate or high risk surgery.
- Prophylaxis of venous thromboembolic disease in bed ridden patients with acute medical illness: heart failure, acute respiratory failure or an episode of acute infection or acute rheumatic disorder associated with at least one additional risk factor for venous thromboembolism.
- Prevention of thrombus formation in the extracorporeal circulation during hemodialysis.

Injectable solution of 60, 80, and 100 mg:
- Treatment of deep venous thrombosis.
- Treatment of acute phase unstable angina and non-Q-wave myocardial infarction, in conjunction with oral aspirin.

**Posology and method of administration**
1 mg (0.1 ml) of enoxaparin corresponds to 100 IU anti XA

**Posology**
Prophylaxis:
The following recommendations generally apply to surgical interventions under general anesthesia.
For techniques of spinal / epidural anesthesia, the need for preoperative injection should be evaluated because of the risk of intraspinal hematoma.

**Frequency of administration:**
One daily injection.

Dose to be administered:
- Surgery with moderate risk for venous thromboembolism: In moderate risk surgery and if patients are not at high risk for venous thromboembolism, a once daily injection of 2000 IU (0.2 ml) provides effective prophylaxis of venous thromboembolic disease. The first injection is to be given almost 2 hours prior to surgery.
- High risk surgery: surgery of the hip and knee. The recommended dosage is 4000 IU (0.4 ml) once daily. The first injection should be given either 2 hours before the intervention when half dose is used, or 12 hours before the intervention when full dose is used.
- Prophylaxis of deep venous thrombosis in bed ridden patients with acute medical illness: the dosage is 4000 IU anti Xa (0.4 ml) (40 mg /0.4 ml) once daily subcutaneously.
- Other situations: Higher prophylactic dosage may be used if the risk related to the type of surgery (mainly for cancer) and / or the patient (especially previous venous thromboembolic disease) is increased.

**Duration of treatment:**
The duration of anticoagulant therapy is related to the risk of venous thromboembolism; in all cases, this treatment in conjunction with usual techniques of lower limb elastic stockings, should be maintained until active and complete patient mobilization. In surgery, the mean duration of heparin therapy will not exceed 10 days.
If long-term anticoagulant treatment is required, as in hip surgery in particular, follow-on treatment may be either heparin or oral anticoagulants. The benefit of prophylaxis with a once daily injection of enoxaparin 4000 IU (0.4 ml) for 4 to 5 weeks after hip surgery has been established. Nevertheless,
the relative risk of each of these therapies is not evaluated yet.

Prophylaxis of deep venous thrombosis in bedridden patients with acute medical illness: the benefit of enoxaparin 40 mg (0.4 ml) once daily subcutaneously has been established for a duration of therapy of 6 to 14 days. No data is available on safety and efficacy of long-term prophylaxis lasting more than 14 days. If risk factors persist, treatment should be changed.

Data concerning patients above 80 years, body weight <40 kg are limited, therefore, this treatment cannot be recommended for such cases.

**Biological monitoring:**
Platelet count is mandatory all during heparin therapy (see Warnings and Precautions for use).
In normal usage conditions, prophylactic dosages of enoxaparin do not modify the activated clotting time (ACT). Therefore, any monitoring based on this test is useless.
In addition, monitoring of anti-Xa activity is not necessary for prophylactic treatment.

* **Hemodialysis (intravascular route):**
In patients undergoing iterative dialysis sessions, the prevention of coagulation in the extracorporeal circulation is obtained with a dose of 100 IU/Kg or 1 mg/kg of enoxaparin administered into the arterial line of the circuit at the beginning of the dialysis session. This dose is usually sufficient for 4 hour dialysis session. If fibrin rings are found in the dialysis device a further dose of 50 to 100 IU/kg may be given according to the time left to end the session. In patients with major risk of hemorrhage (especially pre or postoperative dialysis) or evolutive hemorrhage syndrome, lower doses of 50 IU/kg (double vascular line) or 75 IU/Kg (single vascular line) could be used during dialysis sessions.

* **Curative treatment:**
  * Deep venous thrombosis: any suspicion of deep venous thrombosis should be rapidly documented using adapted assessment methods.
  * Unstable angina and non-Q-Wave myocardial infarction: enoxaparin is administered in conjunction with oral aspirin (100 to 325 mg daily).

- **Frequency of administration:**
  1 injection every 12 hours.
- **Dose to be administered:**
  The dose per injection is 100 IU/Kg.

Attention is driven on lack of LMWH dosage adaptation according to body weight, in patients above 100 mg or below 40 kg.
Lack of LMWH efficacy or haemorrhagic events may occur in these patients; close clinical monitoring is therefore required in such cases.

**Duration of treatment:**
- Deep venous thrombosis: treatment with LMWH should not exceed 10 days including overlap period with antivitamin K (see: Warnings and Precautions for use). Unless contraindicated, oral anticoagulant treatment is initiated as early as possible.
- Unstable angina and non-Q-Wave myocardial infarction: the recommended duration of treatment is 2 to 8 days, until clinical stabilization of the patient.
If thrombolytic treatment is required, in the absence of clinical data on concomitant use of enoxaparin and thrombolytics, it is recommended to stop enoxaparin treatment, and manage the patient in charge according to the usual standard.

**Biological monitoring:**
Platelet count is mandatory all during heparin therapy (see Warnings and Precautions for use).
Anti-Xa activity may be measured (preferably amidolytic method) in order to evaluate the patient individual sensitivity especially in case of lack of clinical efficacy, hemorrhage or renal insufficiency; blood sampling should be made on the second day of treatment between the third and the fourth hour following the injection; values should range between 0.5 and 1 IU anti-Xa/ml.

**Method of administration**
Enoxaparin must be administered: by subcutaneous injection for prophylactic and curative treatment and by intravascular route for hemodialysis.
Enoxaparin is not intended for intramuscular administration.

**Subcutaneous administration technique:** Subcutaneous injection of enoxaparin should be performed, preferably when the patient is lying down, in the subcutaneous cell tissue of the anterolateral and posterolateral abdominal wall, alternating between left and right sides.

**Contraindications**

**Absolute:**
- History of thrombocytopenia induced by enoxaparin or any other heparin, fractionated or unfractonated; its use must be avoided unless needed. Nevertheless, if heparinization is mandatory refer to Warnings and Precautions for use (platelet monitoring, patients with history of heparin induced thrombocytopenia).
- Manifestations or hemorrhagic tendency related to hemostasis disorders; this may not apply for disseminated intravascular coagulation when this is not related to heparin treatment (see: Warnings and precautions for use: platelet monitoring).
- Organ lesion which may bleed.
- Acute septic endocarditis (except those occurring under mechanical prosthesis).
- Hypersensitivity to enoxaparin.

**Relative:**
- Severe renal insufficiency.
- Uncontrolled hypertension.
- Haemorrhagic stroke.
- Acetylsalicylic, NSAIDs, dextran, ticlopidine (see interactions).

**Warnings and precautions for use**

**Warnings**

Quantification: brands of low molecular weight heparins are at concentrations indicated in different systems: non identical units or mg. Therefore, it is important to be particularly vigilant and respect the specific instructions for use of each brand.

**Spinal / epidural anesthesia:** As with other anticoagulants, rare cases of intraspi- nal hematomas resulting in prolonged or permanent paralysis were reported with the concurrent use of enoxaparin and spinal / epidural anesthesia. The risk of these rare events may be higher with the prolonged use of postoperative in dwelling epidural cath. A neurologic monitoring is mandatory.

**Precautions for use**

**Administration:**
Enoxaparin must not be administered by intramuscular route. Caution should be taken in spinal / epidural anesthesia, in the absence of validated therapeutic outline.

**Biological monitoring:**
- Platelet monitoring: The risk of severe heparin induced thrombocytopenia of immune origin, sometimes resulting in thrombosis, exists as well with low molecular weight heparins. It occurs mainly between the fifth and the twenty first day following treatment initiation with heparin (frequency peak around day 10), or earlier if there is history of heparin induced thrombocytopenia. For this reason, these patients should be systematically identified by taking a thorough history. Besides, if heparin is reintroduced, the risk of recurrence may persist several years or even indefinitely. Consequently, platelet count monitoring is required whatever is the treatment indication, and the administered posology:

Three situations may occur:
- patient with no previous heparin induced thrombocytopenia: platelet count is recommended before initiation of therapy than twice per week for 21 days. If a longer treatment is needed in some specific cases, once weekly platelet count monitoring will be maintained until end of therapy. In practice, any significant drop of platelet count (30 to 50% of initial value) should give alert before it reaches a critical threshold. When a drop in platelet count is noticed, one must proceed as follows:
  * immediate monitoring of this count
Since during the initial phase the full effect of antivitamin K is not achieved, heparin must be maintained until the INR is in the therapeutic range, i.e. between 2 and 3.

- Monitoring of anti-Xa activity.
- Hemodialysis: dosage should be adjusted if anti-Xa activity is below 0.4 IU/ml or above 1.2 IU/ml.
- Curative treatment: in case of haemorrhage, renal insufficiency or lack of clinical efficacy, monitoring of anti-Xa activity may be achieved in order to evaluate patients' individual sensitivity.

Blood sampling should be made on the second day of treatment, between the third and the fourth hour following the injection. Therapeutic values range between 0.5 and 1 IU anti-Xa/ml.

Medical conditions at risk:
Enoxaparin should be used with caution in patients with hepatic and/or renal insufficiency, history of peptic ulcer or any organ lesion which may bleed, diabetic retinopathy, and shortly after brain or spinal surgery.

Drug Interactions
Not recommended combinations:
- acetylsalicylic acid (and by extrapolation other salicylates) systemic route in combination with enoxaparin 20 and 40 mg, and analgesic and antipyretic doses in combination with enoxaparin 60, 80 and 100 mg: enhancing hemorrhagic risk (inhibition of platelet function and alteration of gastroduodenal mucosa by salicylates).

Use non salicylated analgesic-antipyretic.
- NSAIDs (systemic route): increased risk of hemorrhage (inhibition of platelet function and alteration of gastroduodenal mucosa by non steroidal antiinflammatory drugs).

If combination cannot be avoided, keep close clinical monitoring.
- Dextran 40 (vascular route): increased risk of hemorrhage (inhibition of platelet function by dextran 40).
- Ticlopidine: increased risk of hemorrhage (inhibition of platelet function by ticlopidine).
Side effects

- Severe thrombocytopenia sometimes resulting in thrombosis have been reported. Its prevalence is still not well estimated.

Thrombocytopenia could be prevented mainly by checking the patient history, systematic platelet count monitoring as well as withdrawal of LMWH before day 10 of treatment.

- Hemorrhage signs mainly occur in the presence of other risk factors; organ lesions with high tendency for bleeding, some drug combinations (see Contraindications, Interactions).

- Rare cases of intraspinal hematomas have been reported with enoxaparin used during spinal / epidural anesthesia, with prolonged use of postoperative in dwelling epidural catheters. These events have lead to neurologic injury of various seriousness, including prolonged or permanent paralysis (see: Warnings and Precautions for use).

- Rare cases of skin necrosis at the injection site have been reported with unfractionated and low-molecular weight heparins. These events are preceded by a purpura, or painful infiltrated eryhematos plaques with or without general signs. In this case, treatment with enoxaparin must be immediately discontinued.

- Small local hematoma at injection site may follow subcutaneous administration. The importance and frequency of these events increase if recommended subcutaneous administration technique is not respected. In some cases one can notice at the injection site the formation of firm nodules which correspond to an inflammatory reaction rather than a cyst of administered heparin. These nodules disappear within few days, and should not be a reason for treatment discontinuation.

- Rare cutaneous or systemic allergic reactions leading, in some cases, to treatment discontinuation.

- Risk of osteoporosis cannot be excluded as with unfractionated heparins, for treatment lasting several months.

- Increase in liver enzymes.

Overdosage

- In case of heavy ingestion of low molecular weight

Combinations to be used with caution:

- Acetylsalicylic acid at doses inhibiting platelet aggregation in the treatment of unstable angina and non-Q-wave myocardial infarction (with enoxaparin 60, 80 and 100 mg): potential risk of haemorrhage. Close clinical monitoring is recommended.

- Glucocorticoids (systemic route and in some cases local administration: intramuscular, intra-articular, cutaneous and rectal): increased risk of haemorrhage due to corticotherapy (gastro intestinal mucosa, vascular fragility) at high doses or in prolonged treatment (exceeding 10 days). If this combination cannot be avoided, enhance monitoring.

Pregnancy and lactation

Pregnancy

Animal studies did not show teratogenic effect of LMWHs. Therefore, malformation in human species is not expected. Actually, substances leading to malformations in human species are shown to be, till now, teratogenic in animals when tested in well conducted studies on 2 animal species.

Prophylactic and preventive treatment during the first trimester:

At present, there is no pertinent clinical data on possible malformative or fetotoxic effect of enoxaparin when administered at prophylactic doses during the first trimester, or at curative doses throughout pregnancy.

Prophylactic treatment during the second and third trimester:

During the second and third trimester, and in a limited number of pregnancies, clinical use of enoxaparin in prophylaxis settings did not show any malformative or fetotoxic effect.

However, complementary studies are needed to evaluate administration consequences in such conditions. Therefore, prophylactic use of enoxaparin during the second and third trimester should be considered only if needed.

Lactation

Because gastro-intestinal absorption in newborn is improbable, treatment with enoxaparin is not contraindicated in nursing mothers.
Maximum plasma activity occurs between the third and the fourth hour. It is expressed in IU anti-Xa and equals 0.18 + 0.04 (following administration of 2000 IU) and 0.43 + 0.11 (following administration of 4000 IU) in prophylaxis.

In curative treatment plasma anti-Xa activity is 1.01 + 0.14 (following administration of 10000 U).

**Distribution:** Following subcutaneous injection, the apparent anti-Xa elimination half-life of enoxaparin is higher than unfractionated heparin and ranges between 3 to 4 hours.

Anti-IIa activity disappears more rapidly than anti-Xa activity with LMWH.

**Metabolism:** enoxaparin is primarily metabolized in the liver (desulfatation, depolymerisation).

**Elimination:** enoxaparin and its metabolites are excreted in urine (non saturated mechanism) and in bile.

**Population at risk:**
- Elderly patients: may show delayed elimination of enoxaparin (half-life 6 to 7 hours).
- In prophylaxis, this modification does not affect doses and frequency of administration of enoxaparin, as long as creatinine clearance in these patients remains in the tolerated limits, i.e. slight alteration. In curative treatment, monitoring of anti-Xa activity is recommended (see: Posology and Method of administration, Warnings and Precautions for use).
- Patients with severe renal insufficiency: during curative treatment, it is mandatory to adjust posology and to monitor plasma anti-Xa activity if creatinine clearance falls below 30 ml/min.
- In patients undergoing hemodialysis: pharmacokinetics parameters are not altered in patient with renal insufficiency undergoing dialysis.
- Pregnancy: transplacentary passage of LMWH is not probable and at present not enough documented (see Pregnancy and Lactation).

**Specific storage conditions**
To be stocked in its package until its use.