For the use only of a Registered Medical Practitioner or a Hospital or Laboratory

This package insert is continually updated; please read carefully when using a new pack

Enoxaparin Sodium Injection I.P.

Pre-Filled syringe
Low Molecular Weight Heparin

Clexane®

Clexane® 20mg/0.2ml
Clexane® 40mg/0.4ml
Clexane® 60mg/0.6ml
Clexane® 80mg/0.8ml

Composition

Per prefilled syringe of	20 mg	40 mg	60 mg	80 mg
Enoxaparin Sodium I.P.	20 mg	40 mg	60 mg	80 mg
Water for injection I.P. to	0.2 ml	0.4 ml	0.6 ml	0.8 ml

Therapeutic or Pharmacological Class
Antithrombotic Agents. Heparin group.
ATC code: B01A B05 (Antithrombotic Agents; Heparin group)

Pharmaceutical Form(s)
Sterile pyrogen-free solution for injections.
Contained in ready-to-use pre-filled syringes.

Indications

- Prophylaxis of venous thrombo-embolic disease in patients undergoing, an orthopedic or general surgery procedure, including cancer surgery, with a moderate or high risk of thromboembolism.
- Prophylaxis of venous thrombo-embolism in medical patients bedridden due to acute illnesses including cardiac insufficiency, respiratory failure, severe infections, rheumatic diseases.
- Treatment of deep vein thrombosis with or without pulmonary embolism.
- Prevention of thrombus formation in extra corporeal circulation during hemodialysis.
- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI)

Dosage and Method of Administration
General

- **Prophylaxis of venous thrombosis in surgical patients:**

Duration and dose of Clexane therapy are based upon patient risk. The thromboembolic risk for individual patient can be estimated using validated risk stratification models.

In patients with a moderate risk of thrombo-embolism, the recommended dose of enoxaparin sodium is 20mg or 40mg once daily by subcutaneous injection. In general surgery, the first injection should be given 2 hours before the surgical procedure.

Enoxaparin sodium treatment is usually prescribed for an average period of 7 to 10 days. A longer treatment duration may be appropriate in some patients and enoxaparin sodium should be continued for as long as there is a risk of venous thromboembolism and until the patient is ambulatory.

In patients with a high risk of thrombo-embolism, the recommended dose of enoxaparin sodium given by subcutaneous injection, is 40 mg once daily, initiated 12 hours prior to surgery or 30mg twice daily, initiated 12 to 24 hours after surgery.

- For patients who undergo major orthopedic surgery with a high venous thromboembolism risk, a thromboprophylaxis up to 5 weeks is recommended.

- For patients who undergo cancer surgery with a high venous thromboembolism risk, a thromboprophylaxis up to 4 weeks is recommended.

For special recommendations concerning dosing intervals for spinal/epidural anesthesia and percutaneous coronary revascularisation procedures: (see Warnings).

- **Prophylaxis of venous thromboembolism in medical patients:**

The recommended dose of enoxaparin sodium is 40 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:**

Enoxaparin sodium can be administered subcutaneously either as a single injection of 1.5 mg/kg or as twice daily injections of 1 mg/kg. In patients with complicated thromboembolic disorders, a dose of 1mg/kg administered twice daily is recommended.

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).

- **Prevention of extra corporeal thrombus during hemodialysis:**

The recommended dose is 1mg/ kg of enoxaparin sodium.

For patients with a high risk of hemorrhage, the dose should be reduced to 0.5 mg/kg for double vascular access or 0.75 mg/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. The effect of this dose is usually sufficient for a 4-hour session; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 0.5 to 1 mg/kg may be given.

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

The recommended dose of enoxaparin sodium is 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.

- **Treatment of acute ST-segment Elevation Myocardial Infarction:**

The recommended dose of enoxaparin sodium is a single IV bolus of 30 mg plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours (max 100 mg for each of the first two SC doses only, followed by 1 mg/kg SC dosing for the remaining doses). For dosage in patients ≥ 75 years of age,(see section Elderly).

When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific) enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and maintained under (75 to 325 mg once daily) unless contraindicated.

The recommended duration of enoxaparin sodium treatment is 8 days or until hospital discharge, whichever comes first.

For patients managed with Percutaneous Coronary Intervention (PCI): If the last enoxaparin sodium SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of enoxaparin sodium should be administered

Special populations

Children

The safety and efficacy of enoxaparin sodium in children has not been established.

Elderly

For treatment of acute ST-segment Elevation Myocardial Infarction in elderly patients ≥ 75 years of age, do not use an initial IV bolus. Initiate dosing with 0.75 mg/kg SC every 12 hours (maximum 75 mg for each of the first two SC doses only, followed by 0.75 mg/kg SC dosing for the remaining doses)

For other indications, no dose reduction is necessary in the elderly, unless kidney function is impaired.

Hepatic impairment
In the absence of clinical studies, caution should be used in hepatically impaired patients.

Renal impairment

- **Severe renal impairment:**

A dosage adjustment is required for patients with severe renal impairment (creatinine clearance < 30 ml/min), according to the following tables, since enoxaparin sodium exposure is significantly increased in this patient population.

The following dosage adjustments are recommended for therapeutic dosage ranges:

Standard Dosing	**Severe renal impairment**
1 mg/kg SC twice daily	1 mg/kg SC once daily
1.5 mg/kg SC once daily	1 mg/kg SC once daily
For treatment of acute STEMI in patients < 75 years of age	
30mg single IV bolus plus a 1mg/kg SC dose followed by 1mg/kg SC twice daily (Max 100mg for each of the first two SC doses)	30mg single IV bolus plus a 1mg/kg SC dose followed by 1mg/kg SC once daily (Max 100mg for first SC dose only)
For treatment of acute STEMI in elderly patients ≥ 75 years of age	
0.75 mg/kg SC twice daily without initial bolus (Max 75mg for each of the first two SC doses)	1 mg/kg SC once daily without initial bolus (Max 100mg for first SC dose only)

The following dosage adjustments are recommended for prophylactic dosage ranges:

Standard Dosing	**Severe renal impairment**
40 mg SC once daily	20 mg SC once daily
20 mg SC once daily	20 mg SC once daily

The recommended dosage adjustments do not apply to the hemodialysis indication.

- **Moderate and mild renal impairment:** Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised.

Spinal/epidural anesthesia

- For patients receiving spinal/epidural anesthesia see section "Warnings" Spinal/epidural anesthesia.

Administration
Subcutaneous injection: Enoxaparin sodium is administered by subcutaneous injection for the prevention of venous thromboembolic disease, treatment of deep vein thrombosis, treatment of unstable angina and non-Q-wave myocardial infarction and treatment of acute ST segment Elevation Myocardial Infarction.

IV bolus injection: For acute ST-segment Elevation Myocardial Infarction, treatment is to be initiated with a single IV bolus injection immediately followed by a subcutaneous injection

Arterial line injection: It is administered through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extra-corporeal circulation during haemodialysis. It must not be administered by the intramuscular route.
The prefilled disposable syringe is ready for immediate use. The use of a tuberculin syringe or equivalent is recommended when using multiple-dose vials to assure withdrawal of the appropriate volume of drug

Subcutaneous injection technique: Injection should be made preferably when the patient is lying down. Enoxaparin sodium is administered by deep subcutaneous injection. Do not expel the air bubble from the syringe before the injection to avoid the loss of drug when using the 20 and 40 mg prefilled syringes. 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 (see Instructions for use).

Intravenous (Bolus) Injection Technique (for acute STEMI indication only):
Enoxaparin sodium should be administered through an intravenous line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of enoxaparin sodium 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 enoxaparin sodium to clear the port of drug. Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

- **Initial 30-mg bolus**
  For the initial 30 mg bolus, using an enoxaparin sodium graduated prefilled syringe, expel the excessive volume to retain only 30 mg (0.3ml) in the syringe. The 30 mg dose can then be directly injected into the intravenous line.

- **Additional bolus for PCI when last SC administration was given more than 8 hours before balloon inflation**

For patients being managed with Percutaneous Coronary Intervention (PCI), an additional IV bolus of 0.3 mg/kg is to be administered if last SC administration was given more than 8 hours before balloon inflation (see Dosage and Administration: Treatment of acute STEMI).

In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug to 3 mg/ml.

To obtain a 3-mg/ml solution, using a 60-mg enoxaparin sodium prefilled syringe, it is recommended to use a 50-ml infusion bag (i.e. using either normal saline solution (0.9%) or 5% dextrose in water) as follows:

Withdraw 30 ml from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 60-mg enoxaparin sodium prefilled syringe into the 20 ml remaining in the bag. Gently mix the contents of the bag. Withdraw the required volume of diluted solution with a syringe for administration into the intravenous line.

After dilution is completed, the volume to be injected can be calculated using the following formula [Volume of diluted solution (ml) = Patient weight (kg) x 0.1] or using the table below. It is recommended to prepare the dilution immediately before use.

Volume to be injected through intravenous line after dilution is completed

Weight [Kg]	Required dose (0.3 mg/kg) [mg]	Volume to inject when diluted to a final concentration of 3 mg/ml [ml]
45	13.5	4.5
50	15	5
55	16.5	5.5
60	18	6
65	19.5	6.5
70	21	7
75	22.5	7.5
80	24	8
85	25.5	8.5
90	27	9
95	28.5	9.5
100	30	10

Contraindications
Hypersensitivity to enoxaparin sodium, heparin or its derivatives including other Low Molecular Weight Heparins.

History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies.

Active major bleeding and conditions with a high risk of uncontrolled hemorrhage, including recent hemorrhagic stroke.

Warnings

- **General**

Low Molecular Weight Heparins should not be used interchangeably since they differ in their manufacturing process, molecular weights, specific anti-Xa activities, units and dosage. This results in differences in pharmacokinetics and associated biological activities (e.g. anti-thrombin activity, and platelet interactions). Special attention and compliance with the instructions for use specific to each proprietary medicinal product are therefore required.

- **Spinal/Epidural Anesthesia**

There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 40 mg once daily or lower. The risk is greater with higher enoxaparin sodium dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional drugs affecting haemostasis such as NSAIDs (see Interactions with other medicinal products or other forms of interaction). The risk also appears to be increased by traumatic or repeated neuraxial puncture or repeated neuraxial puncture or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anaesthesia/analgesia, the pharmacokinetic profile of the drug should be considered (See Section Pharmacokinetics). Placement and removal of the catheter 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 atleast 12 hours after administration of lower doses (20 mg once daily, 30 mg once or twice daily or 40 mg once daily) of enoxaparin, 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. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial haematoma 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 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 <30ml/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 (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day).

Should the physician decide to administer anticoagulation in the context of epidural/spinal anesthesia 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. Patients should be instructed to inform their physician immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

- **Heparin-induced thrombocytopenia**

Use of enoxaparin sodium 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 Contraindications). Circulating antibodies may persist several years.

Enoxaparin sodium is to be used with extreme caution in patients with a history (more than 100 days) of heparin-induced thrombocytopenia without circulating antibodies. The decision to use enoxaparin sodium in such a case must be made only after a careful benefit risk assessment and after non-heparin alternative treatments are considered.

- **Percutaneous coronary revascularisation procedures**

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina and non-Q-wave myocardial infarction and acute ST- segment myocardial infarction, adhere precisely to the intervals recommended between Clexane® Injection 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 IV/SC enoxaparin sodium injection. 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.

- **Pregnant women with mechanical prosthetic heart valves**

The use of Clexane® Injection 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 fetal death. There have been isolated post marketing 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 (see Precautions: Mechanical prosthetic heart valves)**.**

- **Laboratory tests**

At doses used for prophylaxis of venous thromboembolism, enoxaparin sodium does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation or binding of fibrinogen to platelets. At higher doses, increases in aPTT (activated partial thromboplastin time) and ACT (activated clotting time) may occur. Increases in aPTT and ACT are not linearly correlated with increasing enoxaparin sodium antithrombotic activity and therefore are unsuitable and unreliable for monitoring enoxaparin sodium activity

Precautions

- Do not administer by the intramuscular route.

- Hemorrhage: As with other anticoagulants, bleeding may occur at any site (see Adverse Reactions section).

- If bleeding occurs, the origin of the hemorrhage should be investigated and appropriate treatment instituted.

- Enoxaparin sodium, as with any other anticoagulant therapy, 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,
  - recent neuro- or ophthalmologic surgery,
  - concomitant use of medications affecting hemostasis (see Interactions section).

- Mechanical prosthetic heart valves: The use of Clexane® Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal death. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism (see Warnings: Pregnant women with mechanical prosthetic heart valves)**.**

- Haemorrhage in the elderly: No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially patients eighty years of age and older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical monitoring is advised (see Dosage and Administration: Elderly and Pharmacokinetics: Elderly).

- Renal impairment**:** In patients with renal impairment, there is an increase in exposure of enoxaparin sodium which increases the risk of bleeding. Since 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 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised (see Dosage and Administration: Renal impairment and Pharmacokinetics: Renal impairment).

- Low weight: 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), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients (see Pharmacokinetics: Weight).

- Obese Patients: Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses 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.

- Monitoring of platelet counts: The risk of antibody-mediated heparin-induced thrombocytopenia also exists with Low Molecular Weight Heparins. Should thrombocytopenia occur, it usually appears between the 5th and the 21st day following the beginning of enoxaparin sodium treatment. Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during the treatment. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), enoxaparin sodium treatment must be immediately discontinued and the patient switched to another therapy.

Driving a Vehicle or Performing Other Hazardous Tasks
Enoxaparin sodium has no effect on the ability to drive and operate machines.

Interactions
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:
- Systemic salicylates, acetylsalicylic acid, and NSAIDs including ketorolac,
- Dextran 40, ticlopidine and clopidogrel,
- Systemic glucocorticoids,
- Thrombolytics and anticoagulants,
- Other anti-platelet agents including glycoprotein IIb/IIIa antagonists.

If the combination is indicated, enoxaparin sodium should be used with careful clinical and laboratory monitoring when appropriate.

Pregnancy
Animal studies have not shown any evidence of fetotoxicity or teratogenicity. In the pregnant rat, the transfer of ^{35}S-enoxaparin sodium across the maternal placenta to the fetus is minimal.

In humans, there is no evidence that enoxaparin sodium 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 adequate 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. (See also Warnings: Pregnant women with mechanical prosthetic heart valves and Precautions: Mechanical prosthetic heart valves).

Lactation
In lactating rats, the concentration of 35S-enoxaparin sodium or its labelled metabolites in milk is very low. It is not known whether unchanged enoxaparin sodium is excreted in human breast milk. The oral absorption of enoxaparin sodium is unlikely. However, as a precaution, lactating mothers receiving enoxaparin sodium should be advised to avoid breast-feeding.

Adverse Reactions
Enoxaparin has been evaluated in more than 15,000 patients who received enoxaparin in clinical trials. These included 1776 for prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of deep vein thrombosis with or without pulmonary embolism, 1578 for treatment of unstable angina and non-Q-wave myocardial infarction and 10,176 for treatment of acute ST-elevation myocardial infarction.

Enoxaparin sodium regimen administered during these clinical trials varies depending on indications. The enoxaparin sodium dose was 40 mg SC once daily for prophylaxis of deep vein thrombosis following surgery or in acutely ill medical patients with severely restricted mobility. In treatment of deep vein thrombosis (DVT) with or without pulmonary embolism (PE), patients receiving enoxaparin were treated with either a 1 mg/kg SC dose every 12 hours or a 1.5 mg/kg SC dose once a day. In the clinical studies for treatment of unstable angina and non-Q-wave myocardial infarction, doses were 1 mg/kg SC every 12 hours and in the clinical study for treatment of acute ST-segment elevation myocardial infarction enoxaparin sodium regimen was a 30 mg IV bolus followed by 1 mg/kg SC every 12 hours.

The adverse reactions observed in these clinical studies and reported in post-marketing experience are detailed below.
Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000) or not known (cannot be estimated from available data). Post-marketing adverse reactions are designated with a frequency “not known”.

<u>Haemorrhages</u>
In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients[1]). Some of these cases have been fatal.

As with other anticoagulants, haemorrhage may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see Section Precautions and Section Interactions).

[1] - In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event or (2) if accompanied by an haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.

MedDRA system organ class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
Vascular disorders	*Very common*: **Haemorrhage *** *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage ***	*Very common:* **Haemorrhage *** *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**	*Common:* **Haemorrhage *** *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage *** *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**

*: such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastro-intestinal haemorrhage.

Thrombocytopenia and thrombocytosis

MedDRA system organ class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
Blood and lymphatic system disorders	*Very common*: **Thrombocytosis*** *Common:* **Thrombocytopenia**	*Uncommon:* **Thrombocytopenia**	*Very common*: **Thrombocytosis *** *Common:* **Thrombocytopenia**	*Uncommon:* **Thrombocytopenia**	*Common:* **Thrombocytosis* Thrombocytopenia** *Very rare:* **Immuno-allergic thrombocytopenia**

*: Platelet increased > 400 G/L

Other clinically relevant adverse reactions
These reactions are presented below, whatever the indications, by system organ class, frequency grouping and decreasing order of seriousness.

MedDRA system organ class	All indications
Immune system disorders	*Common:* **Allergic reaction** *Rare:* **Anaphylactic / anaphylactoid reaction (see also Post marketing experience)**
Hepatobilary disorders	*Very common:* **Hepatic enzymes increase (mainly transaminases **)**
Skin and subcutaneous tissue disorders	*Common:* **Urticaria, pruritus, erythema,** *Uncommon:* **Bullous dermatitis**
General disorders and administration site conditions	*Common:* **Injection site haematoma, injection site pain, other injection site reaction*** *Uncommon:* **Local irritation; skin necrosis at injection site**
Investigations	*Rare:* **Hyperkaliemia**

*: such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction (NOS)
**: transaminases levels > 3 times the upper limit of normality

Post marketing experience

The following adverse reactions have been identified during post approval use of Clexane®. The adverse reactions are derived from spontaneous reports and therefore, the frequency is "not known" (cannot be estimated from the available data)

- Immune System Disorders
  - Anaphylactic/anaphylactoid reaction including shock
- Nervous System Disorders
  - Headache
- Vascular Disorders
  - Cases of spinal haematoma (or neuraxial haematoma) have been reported with the concurrent use of enoxaparin sodim as well as spinal/epidural anaesthesia or spinal puncture. These reactions have resulted in varying degrees of neurologic injuries including long term or permanent paralysis.
- Blood and Lymphatic System Disorders:
  - Haemorrhagic anemia
  - Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see Precautions: Monitoring of platelet counts).
  - Eosinophilia
- Skin and subcutaneous disorders
  - Cutaneous vasculitis, skin necrosis usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful). Treatment with enoxaparin sodium must be discontinued.
  - Injection site nodules (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.
  - Alopecia
- Hepatobilary disorders
  - Hepatocellular liver injury
  - Cholestatic liver injury
- Musculoskeletal and connective tissue disorders

- Osteoporosis following long-term therapy (greater than 3 months)

Overdosage
Signs and symptoms
- **Symptoms and severity**

Accidental overdosage with enoxaparin sodium after intravenous, extracorporeal or subcutaneous administration may lead to hemorrhagic complications. Following oral administration of even large doses, it is unlikely that enoxaparin sodium will be absorbed.

Management
- **Antidote and treatment**

The anticoagulant effects can be largely neutralized by the slow intravenous injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected; 1 mg protamine neutralizes the anticoagulant effect of 1 mg of 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. After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. However, even with high doses of protamine, the anti-Xa activity of enoxaparin sodium is never completely neutralized (maximum about 60%).

Pharmacodynamics
Enoxaparin sodium is a Low Molecular Weight Heparin with a mean molecular weight of approximately 4,500 daltons. The drug substance is the sodium salt. The molecular weight distribution is:
<2000 daltons ≤ 20%
2000 to 8000 daltons ≥ 68%
>8000 daltons ≤ 18%

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-enepyranosuronic 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 an 1,6 anhydro derivative on the reducing end of the polysaccharide chain. In the *in vitro* purified system, enoxaparin sodium has a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti thrombin activity (approximately 28 IU/mg). These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti-thrombotic activities in humans.

Beyond its anti-Xa/IIa activity, further anti-thrombotic and anti-inflammatory properties of enoxaparin have been identified in healthy subjects and patients as well as in non-clinical models.
These include ATIII-dependent inhibition of other coagulation factors like factor VIIa, induction of endogenous Tissue Factor Pathway Inhibitor (TFPI) release as well as a reduced release of von Willebrand factor (vWF) from the vascular endothelium into the blood circulation. These factors are known to contribute to the overall anti-thrombotic effect of enoxaparin.

- ***Clinical efficacy/ Clinical Studies***

Treatment of unstable angina and non-Q-wave myocardial infarction
In a large multicenter study, 3,171 patients enrolled at the acute phase of unstable angina or non-Q-wave myocardial infarction were randomized to receive in association with aspirin (100 to 325 mg once daily), either subcutaneous enoxaparin sodium 1mg/kg every 12 hours or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (aPTT). Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilization, revascularization procedures or hospital discharge. The patients had to be followed up to 30 days. Enoxaparin sodium compared to heparin significantly decreased the incidence of recurrent angina, myocardial infarction and death, with a relative risk reduction of 16.2% at Day 14, sustained over the 30 day period. Furthermore, fewer patients in the enoxaparin sodium group underwent revascularization with either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) (15.8% relative risk reduction at Day 30).

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI).
In a large multicenter study, 20479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium in a single 30-mg intravenous bolus plus a 1 mg/kg SC dose followed by an SC injection of 1.0 mg/kg every 12 hours or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (aPTT) for 48 hours. All patients were also treated with aspirin for a minimum of 30 days. The enoxaparin dosing strategy was adjusted for severe renally impaired patients and for the elderly of at least 75 years of age. The SC injections of enoxaparin were given until hospital discharge or for a maximum of eight days (whichever came first).

4716 patients underwent percutaneous coronary intervention receiving antithrombotic support with blinded study drug. Therefore, 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 last SC administration given less than 8 hours before balloon inflation, IV bolus of 0.3 mg/kg enoxaparin, if the last SC administration given more than 8 hours before balloon inflation.

Enoxaparin sodium compared to unfractionated heparin significantly decreased the incidence of the primary end point, a composite of death from any cause or myocardial re-infarction in the first 30 days after randomization [9.9 percent in the enoxaparin group, as compared with 12.0 percent in the unfractionated heparin group] with a 17 percent relative risk reduction (P<0.001).

The treatment benefits of enoxaparin, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35 percent reduction in the relative risk of myocardial re-infarction, as compared with treatment with unfractionated heparin (P<0.001).

The beneficial effect of enoxaparin on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, type of fibrinolytic administered, and time to treatment with study drug.

There was a significant treatment benefit of enoxaparin, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomization (23 percent reduction in relative risk) or who were treated medically (15 percent reduction in relative risk, P = 0.27 for interaction). The rate of the 30 day composite endpoint of death, myocardial re-infarction or ICH (a measure of net clinical benefit) was significantly lower (p<0.0001) in the enoxaparin group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favor of treatment with Clexane®.

The beneficial effect of enoxaparin on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period.

Pharmacokinetics

- ***General characteristics***

The pharmacokinetic parameters of enoxaparin sodium have been studied primarily in terms of the time course of plasma anti-Xa activity and also by anti-IIa activity, at the recommended dosage ranges after single and repeated subcutaneous administration and after single intravenous administration. The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by validated amidolytic methods with specific substrates and an enoxaparin standard calibrated against the international standard for LMWHs (NIBSC).

Absorption

- ***Bioavailability and Absorption***

The absolute bioavailability of enoxaparin sodium after subcutaneous injection, based on anti-Xa activity, is close to 100%. Injection volume and dose concentration over the range 100-200 mg/ml does not affect pharmacokinetic parameters in healthy volunteers.

The mean maximum plasma anti-Xa activity is observed 3 to 5 hours after subcutaneous injection and achieves approximately 0.2, 0.4, 1.0 and 1.3 anti-Xa IU/ml following single-subcutaneous administration of 20 mg, 40 mg, 1 mg/kg and 1.5 mg/kg doses, respectively.

A 30 mg IV bolus immediately followed by a 1 mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 88% of steady-state levels. Steady-state is achieved on the second day of treatment.

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges. Intra-patient and inter-patient variability is low. After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once daily 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 3 to 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.

Plasma anti-IIa activity after subcutaneous administration is approximately ten-fold lower than anti-Xa activity. The mean maximum anti-IIa activity is observed approximately 3 to 4 hours following subcutaneous injection and reaches

0.13 IU/ml and 0.19 IU/ml following repeated administration of 1 mg/kg twice daily and 1.5 mg/kg once daily, respectively.

- ***Distribution***

The volume of distribution of enoxaparin sodium anti-Xa activity is about 5 liters and is close to the blood volume.

- ***Metabolism***

Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency.

- ***Elimination***

Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 L/h after a 1.5 mg/kg 6-hour intravenous infusion.
Elimination appears monophasic with a half-life of about 4 hours after a single subcutaneous dose to about 7 hours after repeated dosing.
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***

Elderly
Based on the results of a population pharmacokinetic analysis, the enoxaparin sodium kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see Precautions: Hemorrhage in the Elderly, Dosage and Administration: Elderly, and Pharmacokinetics: Renal impairment).

Renal impairment
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. Anti-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 Precautions: Renal impairment and Dosage and Administration: Renal impairment).

Weight
After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-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. There is a lower weight-adjusted clearance in obese subjects with subcutaneous dosing. 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 (see Precautions: Low Weight).

Hemodialysis
In a single study, elimination rate appeared similar but AUC was two-fold higher than control population, after a single 0.25 or 0.50 mg/kg intravenous dose.

- ***Pharmacokinetic interactions***

No pharmacokinetic interactions were observed between enoxaparin and thrombolytics when administered concomitantly

Incompatibilities / Compatibilities
Subcutaneous injection: Do not admix with other products.

Intravenous (Bolus) Injection (for acute STEMI indication only): Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water

Storage
Store at or below 25°C. Do not freeze prefilled syringes.

Preparation and Handling
See posology and method of administration. The prefilled disposable syringe is ready for immediate use.

Manufactured by:
CHINOIN Pharmaceutical and Chemical Works Private Co. Ltd,
Csanyikvölgy Site Miskolc, Csanyikvölgy, H-3510 Hungary

Marketed by:
Sanofi India Ltd.,
BUILDING NO. B-4, GALA NO. 1A, FIRST FLOOR, CITY LINK WAREHOUSING COMPLEX,
MUMBAI NASHIK HIGHWAY, VILLAGE VADAPE BHIWANDI
Tal: MUMBAI NASHIK HIGHWAY (NH3) (THANE-ZONE2)- 421302

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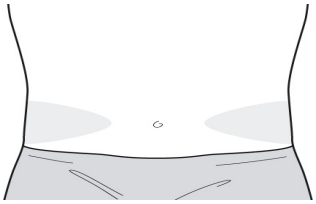
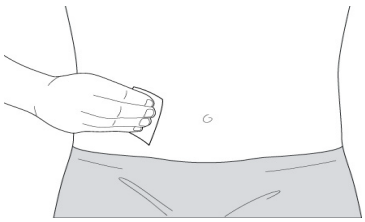
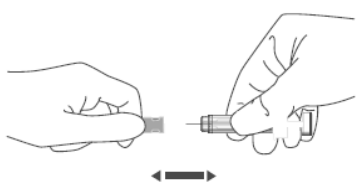
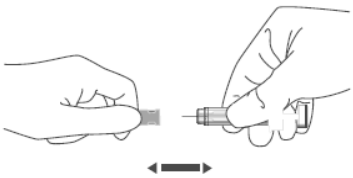
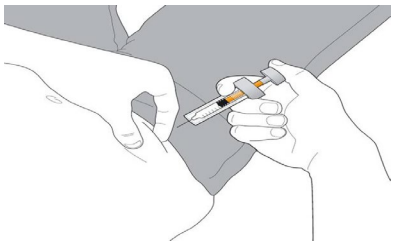
INSTRUCTIONS FOR USE: Subcutaneous injection technique

In case of self-injection, the healthcare professional will show the patient how to administer the injections before the patient is released from hospital. It is essential to follow these instructions exactly. If the patient has questions, be sure to ask the healthcare professional to provide the explanations needed.

Proper subcutaneous (under the skin) injection is essential to prevent pain and bruising at the injection site.

Prepare the site for injection	
	The recommended site for injection is into the fat of the lower abdomen. This should be at least 5 centimetres (2 inches) away from the belly button and out towards either side.
	Prior to injection, wash your hands. Cleanse (do not rub) the selected site for injection with an alcohol swab. Select a different site of lower abdomen for each injection.

Prepare the syringe before the injection Check the expiry date on the label or carton. Do not use if the date has passed. Check the syringe is not damaged and the medicine in it is a clear solution without particle. If the syringe is damaged or the medicine is not clear use another syringe.	
	**For 20 and 40 mg doses:** - Take the protective cap off the needle. A drop may appear at the tip of the needle. If this occurs, remove the drop before injection by tapping on the syringe, with the needle pointing down. The prefilled syringe is ready to use. Do not expel any air from the syringe before administering the injection.

	**For 60 and 80mg prefilled syringes:** - Take the protective cap off the needle. - Adjust the dose to be injected (if necessary): The amount of medicine to be injected must be adjusted depending on the patient's body weight; therefore any excess medicine must be expelled before injection. Hold the syringe pointing down (to keep the air bubble in the syringe) and expel the excess medicine into an appropriate container. When there is no need to adjust the dose, the prefilled syringe is ready to use. Do not expel any air from the syringe before administering the injection. A drop may appear at the tip of the needle. If this occurs, remove the drop before injection by tapping on the syringe, with the needle pointing down.
Administer the injection (all prefilled syringes: 20, 40, 60, 80 mg)	
	While lying down or sitting in a comfortable position, grasp a skin fold between the thumb and index finger.
	Hold the needle at a right angle to the skin fold and inject into the skin fold. This skin fold should be held throughout the injection. Complete the injection using all of the medicine in the syringe.
	Immediately dispose off the syringe in the nearest sharps container.

For more information contact your physician.