



DENORINTM

(Enoxaparin Sodium)

WARNING: SPINAL/EPIDURAL HAEMATOMAS

- Enoxaparin in patients undergoing spinal/epidural anaesthesia or spinal puncture increases the risk of spinal or epidural haematoma, which may cause long-term or permanent paralysis
- Risk is increased by:
 - Indwelling epidural catheters for analgesia
 - Drugs affecting haemostasis [e.g., nonsteroidal anti-inflammatory drugs, platelet inhibitors, anticoagulants]
 - Traumatic or repeated spinal or epidural puncture

1. NAME OF THE PRODUCT

DENORINTM (Enoxaparin Sodium) Injection 4000 anti-Xa IU/0.4ml

DENORINTM (Enoxaparin Sodium) Injection 6000 anti-Xa IU/0.6ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DENORINTM Injection 4000 anti-Xa IU/0.4ml

Each pre-filled syringe contains:

Enoxaparin sodium BP.....40mg

DENORINTM Injection 6000 anti-Xa IU/0.6ml

Each pre-filled syringe contains:

Enoxaparin sodium BP.....60mg

3. PHARMACEUTICAL FORM

Pre-Filled Syringe

Appearance:

DENORINTM Injection 4000 anti-Xa IU/0.4ml: Clear colourless solution free from foreign particles.

DENORINTM Injection 6000 anti-Xa IU/0.6ml: Clear colourless solution free from foreign particles.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

DENORINTM Injection is indicated in adults for:

- Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients, particularly those undergoing orthopedic or general surgery including cancer surgery.



- Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections or rheumatic diseases) and reduced mobility at increased risk of venous thromboembolism.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.
- Extended treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of its recurrence in patients with active cancer.
- Prevention of thrombus formation in extra corporeal circulation during haemodialysis.
- Acute coronary syndrome:
 - Treatment of unstable angina and Non-ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid.
 - Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients:

Individual thromboembolic risk for patients can be estimated using validated risk stratification model.

- In patients at moderate risk of thromboembolism, the recommended dose of enoxaparin sodium is 2,000 IU (20mg) once daily by subcutaneous (SC) injection. Preoperative initiation (2 hours before surgery) of enoxaparin sodium 2,000 IU (20mg) was proven effective and safe in moderate risk surgery.
- In moderate risk patients, enoxaparin sodium treatment should be maintained for a minimal period of 7-10 days whatever the recovery status (e.g., mobility).
- In patients at high risk of thromboembolism, the recommended dose of enoxaparin sodium is 4,000 IU (40mg) once daily given by SC injection preferably started 12 hours before surgery. If there is a need for earlier than 12 hours enoxaparin sodium preoperative prophylactic initiation (e.g., high risk patient waiting for a deferred orthopedic surgery), the last injection should be administered no later than 12 hours prior to surgery and resumed 12 hours after surgery.
 - For patients who undergo major orthopedic surgery an extended thromboprophylaxis up to 5 weeks is recommended.



- For patients with a high venous thromboembolism (VTE) risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks is recommended.

Prophylaxis of venous thromboembolism in medical patients:

The recommended dose of enoxaparin sodium is 4,000 IU (40mg) once daily by SC injection. Treatment with enoxaparin sodium is prescribed for at least 6 to 14 days whatever the recovery status (e.g., mobility). The benefit is not established for treatment longer than 14 days.

Treatment of DVT and PE: Enoxaparin sodium can be administered SC either as a once daily injection of 150 IU/kg (1.5mg/kg) or as twice daily injections of 100 IU/kg (1mg/kg). The regimen should be selected by the physician based on an individual assessment including evaluation of the thromboembolic risk and of the risk of bleeding. The dose regimen of 150 IU/kg (1.5mg/kg) administered once daily should be used in uncomplicated patients with low risk of VTE recurrence. The dose regimen of 100 IU/kg (1mg/kg) administered twice daily should be used in all other patients such as those with obesity, with symptomatic PE, cancer, recurrent VTE or proximal (vena iliaca) thrombosis. Enoxaparin sodium treatment is prescribed for an average period of 10 days. Oral anticoagulant therapy should be initiated when appropriate. In the extended treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of its recurrence in patients with active cancer, physicians should carefully assess the individual thromboembolic and bleeding risks of the patient. The recommended dose is 100 IU/kg (1mg/kg) administered twice daily by SC injections for 5 to 10 days, followed by a 150 IU/kg (1.5mg/kg) once daily SC injection up to 6 months. The benefit of continuous anticoagulant therapy should be reassessed after 6 months of treatment.

Prevention of thrombus formation during haemodialysis: The recommended dose is 100 IU/kg (1mg/kg) of enoxaparin sodium. For patients with a high risk of haemorrhage, the dose should be reduced to 50 IU/kg (0.5mg/kg) for double vascular access or 75 IU/kg (0.75mg/kg) for single vascular access. During haemodialysis, 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 50 – 100 IU/kg (0.5 – 1mg/kg) may be given.

Acute coronary syndrome: treatment of unstable angina and NSTEMI and treatment of acute STEMI:

- For treatment of unstable angina and NSTEMI, the recommended dose of enoxaparin sodium is 100 IU/kg (1mg/kg) every 12 hours by SC injection administered in combination with antiplatelet therapy. Treatment should be maintained for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days. Acetylsalicylic acid is recommended for all patients without contraindications at an initial



oral loading dose of 150–300mg (in acetylsalicylic acid-naive patients) and a maintenance dose of 75–325mg/day long-term regardless of treatment strategy.

- For treatment of acute STEMI, the recommended dose of enoxaparin sodium is a single intravenous (IV) bolus of 3,000 IU (30mg) plus a 100 IU/kg (1mg/kg) SC dose followed by 100 IU/kg (1mg/kg) administered SC every 12 hours (maximum 10,000 IU (100mg) for each of the first two SC doses). Appropriate antiplatelet therapy such as oral acetylsalicylic acid (75mg to 325mg once daily) should be administered concomitantly unless contraindicated. The recommended duration of treatment is 8 days or until hospital discharge, whichever comes first. 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.
 - For patients managed with PCI, if the last dose of enoxaparin sodium SC 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 30 IU/kg (0.3mg/kg) enoxaparin sodium should be administered.

Paediatric population: The safety and efficacy of enoxaparin sodium in paediatric population have not been established.

Elderly: For all indications except STEMI, no dose reduction is necessary in the elderly patients, unless kidney function is impaired. For treatment of acute STEMI in elderly patients ≥ 75 years of age, an initial IV bolus must not be used. Initiate dosing with 75 IU/kg (0.75mg/kg) SC every 12 hours (maximum 7,500 IU (75mg) for each of the first two SC doses only, followed by 75 IU/kg (0.75mg/kg) SC dosing for the remaining doses).

Hepatic impairment: Limited data are available in patients with hepatic impairment and caution should be used in these patients.

Renal impairment:

- **Severe renal impairment:** Enoxaparin sodium is not recommended for patients with end stage renal disease (creatinine clearance < 15 ml/min) due to lack of data in this population outside the prevention of thrombus formation in extra corporeal circulation during haemodialysis.

Dosage table for patients with severe renal impairment (creatinine clearance [15-30] mL/min):

Indication	Dosing regimen
Prophylaxis of venous thromboembolic disease	2,000 IU (20mg) SC once daily
Treatment of DVT and PE	100 IU/kg (1mg/kg) body weight SC once daily



Extended treatment of DVT and PE in patients with active cancer	100 IU/kg (1mg/kg) body weight SC once daily
Treatment of unstable angina and NSTEMI	100 IU/kg (1mg/kg) body weight SC once daily
Treatment of acute STEMI (patients under 75)	1 x 3,000 IU (30mg) IV bolus plus 100 IU/kg (1mg/kg) body weight SC and then 100 IU/kg (1mg/kg) body weight SC every 24 hours
Treatment of acute STEMI (patients over 75)	No IV initial bolus, 100 IU/kg (1mg/kg) body weight SC and then 100 IU/kg (1mg/kg) body weight SC every 24 hours

The recommended dosage adjustment do not apply to the haemodialysis indication.

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

Method of administration:

Enoxaparin sodium should not be administered by the intramuscular route.

- For the prophylaxis of venous thrombo-embolic disease following surgery, treatment of DVT and PE, extended treatment of DVT and PE in patients with active cancer, treatment of unstable angina and NSTEMI, enoxaparin sodium should be administered by SC injection.
- For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection.
- For the prevention of thrombus formation in the extra corporeal circulation during haemodialysis, it is administered through the arterial line of a dialysis circuit.

The pre-filled disposable syringe is ready for immediate use.

SC injection technique: Injection should be made preferably when the patient is lying down. Enoxaparin sodium is administered by deep SC injection. Do not expel the air bubble from the syringe before the injection to avoid the loss of drug when using pre-filled syringes. When the quantity of drug to be injected requires to be adjusted based on the patient's body weight, use the graduated pre-filled syringes to reach the required volume by discarding the excess before injection. Please be aware that in some cases it is not possible to achieve an exact dose due to the graduations on the syringe, and in such case the volume shall be rounded up to the nearest graduation. 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.

Note for the pre-filled syringes fitted with an automatic safety system: The safety system is triggered at the end of the injection. In case of self-administration, patient should be advised to follow instructions provided in the patient information leaflet included in the pack of this medicine.

IV (bolus) injection (for acute STEMI indication only): For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection. For IV injection, either the multidose vial or pre-filled syringe can be used. Enoxaparin sodium should be administered through an IV line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of enoxaparin sodium with other drugs, the IV access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the IV 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 3,000 IU (30mg) bolus:** For the initial 3,000 IU (30mg) bolus, using an enoxaparin sodium graduated pre-filled syringe, expel the excessive volume to retain only 3,000 IU (30mg) in the syringe. The 3,000 IU (30mg) dose can then be directly injected into the IV line.
- **Additional bolus for PCI when last SC administration was given more than 8 hours before balloon inflation:** For patients being managed with PCI, an additional IV bolus of 30 IU/kg (0.3mg/kg) is to be administered if last SC administration was given more than 8 hours before balloon inflation. In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug to 300 IU/mL (3mg/mL). To obtain a 300 IU/mL (3mg/mL) solution, using a 6,000 IU (60mg) enoxaparin sodium pre-filled 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 30mL from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 6,000 IU (60mg) enoxaparin sodium pre-filled syringe into the 20mL 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 IV line.
- After dilution is completed, the volume to be injected can be calculated using the following formula:

$$[\text{Volume of diluted solution (mL)} = \text{Patient weight (kg)} \times 0.1]$$

or using the table below. It is recommended to prepare the dilution immediately before use.

Volume to be injected through IV line after dilution is completed at a concentration of 300 IU (3mg)/ml



Weight	Required dose 30 IU/kg (0.3mg/kg)		Volume to inject when diluted to a final concentration of 300 IU (3mg)/mL
	[kg]	IU	[mg]
45	1350	13.5	4.5
50	1500	15	5
55	1650	16.5	5.5
60	1800	18	6
65	1950	19.5	6.5
70	2100	21	7
75	2250	22.5	7.5
80	2400	24	8
85	2550	25.5	8.5
90	2700	27	9
95	2850	28.5	9.5
100	3000	30	10
105	3150	31.5	10.5
110	3300	33	11
115	3450	34.5	11.5
120	3600	36	12
125	3750	37.5	12.5
130	3900	39	13
135	4050	40.5	13.5
140	4200	42	14
145	4350	43.5	14.5
150	4500	45	15

- **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.

Switch between enoxaparin sodium and oral anticoagulants:

- **Switch between enoxaparin sodium and vitamin K antagonists (VKA):** Clinical monitoring and laboratory tests [prothrombin time expressed as the International Normalized Ratio (INR)] must be intensified to monitor the effect of VKA. As there is an interval before the VKA reaches its maximum effect, enoxaparin sodium therapy should be continued at a constant dose for as long as necessary in order to maintain the INR within the desired therapeutic range for the indication in two successive tests. For patients currently receiving a VKA, the VKA should be discontinued and the first dose of enoxaparin sodium should be given when the INR has dropped below the therapeutic range.



- **Switch between enoxaparin sodium and direct oral anticoagulants (DOAC):** For patients currently receiving enoxaparin sodium, discontinue enoxaparin sodium and start the DOAC 0 to 2 hours before the time that the next scheduled administration of enoxaparin sodium would be due as per DOAC label. For patients currently receiving a DOAC, the first dose of enoxaparin sodium should be given at the time the next DOAC dose would be taken.

Administration in spinal/epidural anaesthesia or lumbar puncture: Should the physician decide to administer anticoagulation in the context of epidural or spinal anaesthesia/analgesia or lumbar puncture, careful neurological monitoring is recommended due to the risk of neuraxial haematomas.

At doses used for prophylaxis:

- A puncture-free interval of at least 12 hours shall be kept between the last injection of enoxaparin sodium at prophylactic doses and the needle or catheter placement.
- For continuous techniques, a similar delay of at least 12 hours should be observed before removing the catheter.
- For patients with creatinine clearance [15-30] mL/min, consider doubling the timing of puncture/catheter placement or removal to at least 24 hours.
- The 2 hours preoperative initiation of enoxaparin sodium 2,000 IU (20mg) is not compatible with neuraxial anaesthesia.

At doses used for treatment:

- A puncture-free interval of at least 24 hours shall be kept between the last injection of enoxaparin sodium at curative doses and the needle or catheter placement.
- For continuous techniques, a similar delay of 24 hours should be observed before removing the catheter.
- For patients with creatinine clearance [15-30] mL/min, consider doubling the timing of puncture/catheter placement or removal to at least 48 hours.
- Patients receiving the twice daily doses (i.e., 75 IU/kg (0.75mg/kg) twice daily or 100 IU/kg (1mg/kg) twice-daily) should omit the second enoxaparin sodium dose to allow a sufficient delay before catheter placement or removal.

Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial hematoma will be avoided. Consider not using enoxaparin sodium until at least 4 hours after the spinal/epidural puncture or after the catheter has been removed. The delay must be 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.

4.3. CONTRAINDICATIONS:

Enoxaparin sodium is contraindicated in patients with:



- Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including other low molecular weight heparins (LMWH) or to any of the excipients.
- History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies.
- Active clinically significant bleeding and conditions with a high risk of haemorrhage, including recent haemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Spinal or epidural anaesthesia or loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24 hours.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

General: Enoxaparin sodium cannot be used interchangeably (unit for unit) with other LMWHs. These medicinal products differ in their manufacturing process, molecular weights, specific anti-Xa and anti-IIa activities, units, dosage and clinical efficacy and safety. 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.

History of HIT (>100 days): 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. Circulating antibodies may persist several years. Enoxaparin sodium is to be used with extreme caution in patients with a history (>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 (e.g., danaparoid sodium or lepirudin).

Monitoring of platelet counts: In patients with cancer with a platelet count below 80g/L, anticoagulation treatment can only be considered on a case-by-case basis and careful monitoring is recommended. The risk of antibody-mediated HIT also exists with LMWHs. The risk of HIT is higher in postoperative patients and mainly after cardiac surgery and in patients with cancer. It is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during the treatment. If a confirmed significant decrease of the platelet count is observed (30 – 50% of the initial value), enoxaparin sodium treatment must be immediately discontinued.

Haemorrhage: As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the haemorrhage 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 haemostasis
- History of peptic ulcer
- Recent ischemic stroke
- Severe arterial hypertension
- Recent diabetic retinopathy
- Neuro- or ophthalmologic surgery
- Concomitant use of medications affecting haemostasis

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 activated partial thromboplastin time (aPTT), and activated clotting time (ACT) 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.

Spinal/Epidural anaesthesia or lumbar puncture: Spinal/epidural anaesthesia or lumbar puncture must not be performed within 24 hours of administration of enoxaparin sodium at therapeutic doses. There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture procedures resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 4,000 IU (40mg) once daily or lower. The risk of these events is higher with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting haemostasis such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), with traumatic or repeated epidural or spinal 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 or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin sodium is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. For patients with creatinine clearance [15-30mL/minute], additional considerations are necessary because elimination of enoxaparin sodium is more prolonged. 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. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for



spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

Skin necrosis / cutaneous vasculitis: Skin necrosis and cutaneous vasculitis have been reported with LMWHs and should lead to prompt treatment discontinuation.

Percutaneous coronary revascularization procedures: To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, NSTEMI and acute STEMI, adhere precisely to the intervals recommended between enoxaparin sodium injection doses. It is important to achieve haemostasis 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 haematoma formation.

Acute infective endocarditis: Use of heparin is usually not recommended in patients with acute infective endocarditis due to the risk of cerebral haemorrhage. If such use is considered absolutely necessary, the decision must be made only after a careful individual benefit risk assessment.

Mechanical prosthetic heart valves: The use of enoxaparin sodium has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. In some pregnant women thrombosis led to maternal and foetal death.

Pregnant women with mechanical prosthetic heart valves: The use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism.

Elderly: 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 and dose reduction might be considered in patients older than 75 years treated for STEMI

Renal impairment: In patients with renal impairment, there is an increase in exposure of enoxaparin sodium which increases the risk of bleeding. In these patients, careful clinical monitoring is advised, and biological monitoring by anti-Xa activity measurement might be considered. Enoxaparin sodium is not recommended for patients with end stage renal disease (creatinine clearance <15ml/min). In patients with severe renal impairment (creatinine clearance 15-30mL/min), since exposure of enoxaparin sodium is significantly increased, a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dose adjustment is recommended in patients with moderate (creatinine clearance 30-50mL/min) and mild (creatinine clearance 50-80mL/min) renal impairment.



Hepatic impairment: Enoxaparin sodium should be used with caution in patients with hepatic impairment due to an increased potential for bleeding. Dose adjustment based on monitoring of anti-Xa levels is unreliable in patients with liver cirrhosis and not recommended.

Low weight: An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45kg) and low-weight men (<57kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients.

Obese Patients: Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30kg/m²) 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.

Hyperkalaemia: Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, taking medicinal products known to increase potassium. Plasma potassium should be monitored regularly especially in patients at risk.

Traceability: LMWHs are biological medicinal products. In order to improve the LMWH traceability, it is recommended that health care professionals record the trade name and batch number of the administered product in the patient file.

Acute generalized exanthematous pustulosis: Acute generalized exanthematous pustulosis (AGEP) has been reported with frequency not known in association with enoxaparin treatment. If signs and symptoms suggestive of these reactions appear, enoxaparin should be withdrawn immediately and an alternative treatment considered (as appropriate).

Sodium content: For patients receiving doses higher than 210mg/day, this medicine contains more than 24mg sodium in each dose. This is equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS

Concomitant use not recommended:

Medicinal products affecting haemostasis: It is recommended that some agents which affect haemostasis should be discontinued prior to enoxaparin sodium therapy unless strictly indicated. If the combination is indicated, enoxaparin sodium should be used with careful clinical and laboratory monitoring when appropriate. These agents include medicinal products such as:

- Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac,



- Other thrombolytics (e.g., alteplase, reteplase, streptokinase, tenecteplase, urokinase) and anticoagulants.

Concomitant use with caution:

The following medicinal products may be administered with caution concomitantly with enoxaparin sodium:

Other medicinal products affecting haemostasis such as:

- Platelet aggregation inhibitors including acetylsalicylic acid used at antiaggregant dose (cardioprotection), clopidogrel, ticlopidine, and glycoprotein IIb/IIIa antagonists indicated in acute coronary syndrome due to the risk of bleeding
- Dextran 40
- Systemic glucocorticoids

Medicinal products increasing potassium levels: Medicinal products that increase serum potassium levels may be administered concurrently with enoxaparin sodium under careful clinical and laboratory monitoring.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: There are no clinical data for enoxaparin sodium in fertility. Animal studies did not show any effect on fertility.

Pregnancy: In humans, there is no evidence that enoxaparin crosses the placental barrier during the second and third trimester of pregnancy. There is no information available concerning the first trimester. Enoxaparin sodium should be used during pregnancy only if the physician has established a clear need. Pregnant women receiving enoxaparin sodium should be carefully monitored for evidence of bleeding or excessive anticoagulation and should be warned of the haemorrhagic risk. If an epidural anaesthesia is planned, it is recommended to withdraw enoxaparin sodium treatment before.

Breast-feeding: It is not known whether unchanged enoxaparin is excreted in human breast milk. In lactating rats, the passage of enoxaparin or its metabolites in milk is very low. The oral absorption of enoxaparin sodium is unlikely. Enoxaparin can be used during breast-feeding.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Enoxaparin sodium has no or negligible influence on the ability to drive and use machines.

4.8. UNDESIRABLE EFFECTS:

The adverse reactions observed in clinical studies and reported in post-marketing experience (* indicates reactions from post-marketing experience) are detailed below. Frequencies are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); not known (cannot be estimated from the



available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders:

Common: Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis

Rare: Eosinophilia*, cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia.

Immune system disorders:

Common: Allergic reaction.

Rare: Anaphylactic/Anaphylactoid reactions including shock*.

Nervous system disorders:

Common: Headache*.

Vascular disorders:

Rare: Spinal haematoma* (or neuraxial haematoma). These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis.

Hepatobiliary disorders:

Very common: Hepatic enzyme increases (mainly transaminases > 3 times the upper limit of normality).

Uncommon: Hepatocellular liver injury*.

Rare: Cholestatic liver injury*.

Skin and subcutaneous tissues disorders:

Common: Urticaria, pruritus, erythema.

Uncommon: Bullous dermatitis.

Rare: Alopecia*, cutaneous vasculitis*, skin necrosis* usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful). Injection site nodules* (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.

Not Known: Acute generalized exanthematous pustulosis (AGEP).

Musculoskeletal and connective tissue disorders:

Rare: Osteoporosis* following long term therapy (greater than 3 months).

General disorders and administration site conditions:

Common: Injection site haematoma, injection site pain, other injection site reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction).

Uncommon: Local irritation, skin necrosis at injection site.

Investigations:

Rare: Hyperkalaemia*.

Description of selected adverse reactions:

Haemorrhages: These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients). Some of these cases have been fatal. In



surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by haemoglobin decrease $\geq 2\text{g/dL}$ or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major. 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.

System Organ Class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Extended treatment of DVT and PE in patients with active cancer	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
Blood and lymphatic system disorders	<i>Very common:</i> Haemorrhage ^a <i>Rare:</i> Retroperitoneal haemorrhage	<i>Common:</i> Haemorrhage ^a	<i>Very common:</i> Haemorrhage ^a <i>Uncommon:</i> Intracranial haemorrhage, Retroperitoneal haemorrhage	<i>Common</i> ^b : Haemorrhage	<i>Common:</i> Haemorrhage ^a <i>Rare:</i> Retroperitoneal haemorrhage	<i>Common:</i> Haemorrhage ^a <i>Uncommon:</i> Intracranial haemorrhage, Retroperitoneal haemorrhage

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

^b: frequency based on a retrospective study on a registry including 3526 patients

Thrombocytopenia and thrombocytosis:

System Organ Class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Extended treatment of DVT and PE in patients with active cancer	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
Blood and lymphatic system disorders	<i>Very common:</i> Thrombocytosis ^c <i>Common:</i> Thrombocytopenia	<i>Uncommon:</i> Thrombocytopenia	<i>Very common:</i> Thrombocytosis ^c <i>Common:</i> Thrombocytopenia	<i>Unknown:</i> Thrombocytopenia	<i>Uncommon:</i> Thrombocytopenia	<i>Common:</i> Thrombocytosis ^c Thrombocytopenia <i>Very rare:</i> Immuno-allergic thrombocytopenia

^c: Platelet increased $>400\text{ G/L}$

4.9. OVERDOSE

Signs and symptoms: Accidental overdose with enoxaparin sodium after IV, extracorporeal or SC administration may lead to haemorrhagic complications. Following oral administration of even large doses, it is unlikely that enoxaparin sodium will be absorbed.

Management: The anticoagulant effects can be largely neutralized by the slow IV injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected; 1mg protamine neutralizes the anticoagulant effect of 100 IU (1mg) of enoxaparin sodium, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5mg protamine per 100 IU (1mg) 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%) (see the prescribing information for protamine salts).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antithrombotic agent, heparin group.

ATC code: B01A B05

Mechanism of action: Enoxaparin is a low molecular weight heparin which has antithrombotic properties.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption: The absolute bioavailability of enoxaparin sodium after SC injection, based on anti-Xa activity, is close to 100%. Different doses and formulations and dosing regimens can be used. The mean maximum plasma anti-Xa activity level is observed 3 to 5 hours after SC injection and achieves approximately 0.2, 0.4, 1.0 and 1.3 anti-Xa IU/mL following single SC administration of 2,000 IU, 4,000 IU, 100 IU/kg and 150 IU/kg (20mg, 40mg, 1mg/kg and 1.5mg/kg) doses, respectively.

Distribution: The volume of distribution of enoxaparin sodium anti-Xa activity is about 4.3 litres and is close to the blood volume.

Biotransformation: 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 150 IU /kg (1.5mg/kg) 6-hour IV infusion. Elimination appears monophasic with a half-life of about 5 hours after a single SC 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.

5.3. PRECLINICAL SAFETY DATA:

Besides the anticoagulant effects of enoxaparin sodium, there was no evidence of adverse effects at 15mg/kg/day in the 13-week SC toxicity studies both in rats and dogs and at 10mg/kg/day in the 26-week SC and IV toxicity studies both in rats, and monkeys. Enoxaparin sodium has shown no mutagenic activity based on in vitro tests, including the Ames test, mouse lymphoma cell forward mutation test, and no clastogenic activity based on an in vitro human lymphocyte chromosomal aberration test, and the in vivo rat bone marrow chromosomal aberration test. Studies conducted in pregnant rats and rabbits at SC doses of enoxaparin sodium up to 30mg/kg/day did not reveal any evidence



of teratogenic effects or foetotoxicity. Enoxaparin sodium was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20mg/kg/day.

6. PHARMACEUTICAL PROPERTIES

6.1. LIST OF EXCIPIENTS:

DENORIN™ Injection 4000 anti-Xa IU/0.4ml: Water for Injection

DENORIN™ Injection 6000 anti-Xa IU/0.6ml: Water for Injection

6.2. INCOMPATIBILITIES:

SC injection:

Do not mix with other products.

IV (Bolus) Injection (for acute STEMI indication only):

This medicinal product must not be mixed with other medicinal product except following:

- Normal saline (0.9%)
- 5% dextrose in water

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and freezing. Store between 15 to 30°C.

Improper storage may deteriorate the medicine.

Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

DENORIN™ Injection 4000 anti-Xa IU/0.4ml:

1ml Pre-filled Glass (USP Type-I) Syringes with chlorobutyl rubber stopper.

Pack size is 0.4ml x 2 Pre-filled Syringes.

DENORIN™ Injection 6000 anti-Xa IU/0.6ml:

1ml Pre-filled Glass (USP Type-I) Syringes with chlorobutyl rubber stopper.

Pack size is 0.6ml x 2 Pre-filled Syringes.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Each syringe is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Injection should not be used if PFS is leaking, solution is discolored, cloudy or it contains undissolved particle(s).

6.7. DRUG PRODUCT SPECIFICATIONS:

DENORIN™ Injection 4000 anti-Xa IU/0.4ml: BP Specs.

DENORIN™ Injection 6000 anti-Xa IU/0.6ml: BP Specs.



7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:



SAMI Pharmaceuticals (Pvt.) Ltd.

F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan

www.samipharma.com

Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

DENORIN™ Injection 4000 anti-Xa IU/0.4ml: 120512

DENORIN™ Injection 6000 anti-Xa IU/0.6ml: 120513

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

DENORIN™ Injection 4000 anti-Xa IU/0.4ml: 24th June, 2025

DENORIN™ Injection 6000 anti-Xa IU/0.6ml: 24th June, 2025

10. DATE OF REVISION OF THE TEXT

ڈی نورن™ انجکشن
(انوکساپیرن سوڈیم)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور منجمد ہونے سے محفوظ رکھیں ۱۵ سے ۳۰ ڈگری سینٹی گریڈ

کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

PFS کے لیک ہونے، محلول کارنگ تبدیل ہونے، دُھندلا ہونے یا

اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

R.N-02/QC/05/2026_SmPC