105 mm 105 mm 105 mm 105 mm 105 mm 105 mm 105 mm 51 mm

30 mm 38 mm 38 mm 38 mm 38 mm 38 mm 38 mm 296 mm

Vaxcel®

ENOXAPARIN SODIUM

SOLUTION FOR INJECTION IN PREFILLED SYRINGE

COMPOSITION:

Active ingredient: enoxaparin sodium.
Solvent: water for injections
Each ml of the solution contains 10000 anti-Xa IU equivalent to 100 mg enoxaparin sodium. One mg (0.01 ml) of enoxaparin sodium corresponds approximately to 100 anti-Xa IU.
Vaxcel Enoxaparin Sodium 2000 IU (20mg)/0.2ml Injection Prefilled Syringe is equivalent to 20 mg, Single-Dose Prefilled Syringes
Vaxcel Enoxaparin Sodium 4000 IU (40mg)/0.4ml Injection Prefilled Syringe is equivalent to 40 mg, Single-Dose Prefilled Syringes
Vaxcel Enoxaparin Sodium 6000 IU (60mg)/0.6ml Injection Prefilled Syringe is equivalent to 60 mg, Single-Dose Graduated Prefilled Syringes

PRESENTATION:

Enoxaparin sodium injection is a clear, colorless to pale yellow sterile solution.

VAXCEL ENOXAPARIN SODIUM INJECTION PREFILLED SYRINGE is biosimilar" to CLEXANE® (enoxaparin sodium)" for the indications listed.

Vaxcel Enoxaparin Sodiumi Injection has been developed as a similar biological medicinal product to Clexane and has been shown to have a comparable quality, safety and efficacy profile to Clexane. Interchangeability is regarded as a matter of clinical practice. See the Position Statements on the Use of Biosimilar in the Ministry of Health and Malaysia Healthcare Facilities serve as a reference for the use of biosimilars in clinical setting.

INDICATIONS:

Vaxcel Enoxaparin Sodium Injection Prefilled Syringe is indicated in adults for:

- Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery.
- Prevention of thrombus formation in extracorporeal circulation during haemodialysis.
- Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infectious pneumopathy, 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 cancer.
- 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).

DOSAGE AND ADMINISTRATION:

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 2000 IU (20 mg) once daily by subcutaneous (SC) injection. Preoperative initiation (2 hours before surgery) of enoxaparin sodium 2000 IU (20 mg) 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). The treatment should be continued until the patient no longer has significantly reduced mobility.
- In patients at high risk of thromboembolism, the recommended dose of enoxaparin sodium is 4000 IU (40 mg) 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 orthopaedic 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 orthopaedic 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 4000 IU (40 mg) 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 a 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 (1.5 mg/kg) or as twice daily injections of 100 IU/kg (1 mg/kg). The regimen should be selected by the physician based on an individual assessment including evaluation of the thrombotic risk and of the risk of bleeding. The dose regimen of 150 IU/kg (1.5 mg/kg) administered once daily should be used in uncomplicated patients with low risk of VTE recurrence. The dose regimen of 100 IU/kg (1 mg/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 (see "Switch between enoxaparin sodium and oral anticoagulants" at the end of section Dosage and Administration).

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 (1 mg/kg) administered twice daily by SC injections for 5 to 10 days, followed by a 150 IU/kg (1.5 mg/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 hemodialysis

The recommended dose is 100 IU/kg (1 mg/kg) of enoxaparin sodium.
For patients with a high risk of hemorrhage, the dose should be reduced to 50 IU/kg (0.5 mg/kg) for double vascular access or 75 IU/kg (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 50 IU to 100 IU/kg (0.5 to 1 mg/kg) may be given.
No data are available in patients using enoxaparin sodium for prophylaxis or treatment and during hemodialysis sessions.

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 (1 mg/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 150–300 mg (in acetylsalicylic acid-naive patients) and a maintenance dose of 75–325 mg/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 3000 IU (30 mg) plus a 100 IU/kg (1 mg/kg) SC dose followed by SC every 12 hours (1 mg/kg) administered SC every 12 hours (maximum 10000 IU (100 mg) for each of the first two SC doses). Appropriate antiplatelet therapy such as oral acetylsalicylic acid (75 mg to 325 mg 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 dosage in patients ≥ 75 years of age, see paragraph "Elderly".
  – 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 (0.3 mg/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 (0.75 mg/kg) SC every 12 hours (maximum 7 500 IU (75 mg) for each of the first two SC doses only, followed by 75 IU/kg (0.75 mg/kg) SC dosing for the remaining doses). For dosage in elderly patients with impaired kidney function, see below "renal impairment" and section Warnings and precautions.

Hepatic impairment

Limited data are available in patients with hepatic impairment (see sections Pharmacodynamic and pharmacokinetic) and caution should be used in these patients (see section Warnings and precautions).

Renal impairment (see sections Warnings and precautions and pharmacokinetic)

- 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	2000 IU (20 mg) SC once daily
Treatment of DVT and PE	100 IU/kg (1 mg/kg) body weight SC once daily
Extended treatment of DVT and PE in patients with active cancer	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of unstable angina and NSTEMI	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of acute STEMI (patients under 75)	1 x 3000 IU (30mg) IV bolus plus 100 IU/kg (1 mg/kg) body weight SC and then 100 IU/kg (1 mg/kg) body weight SC every 24 hours
Treatment of acute STEMI (patients over 75)	No IV initial bolus, 100 IU/kg (1 mg/kg) body weight SC and then 100 IU/kg (1 mg/kg) body weight SC every 24 hours

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

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

ROUTE OF ADMINISTRATION:

Vaxcel Enoxaparin Sodium Injection 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 expel 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 held between the thumb and index finger. This skin fold should not be released until the injection is complete. Do not rub the injection site after administration.
- IV (bolus) injection (for acute STEMI indication only):
  Treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection.
  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 3000 IU (30 mg) bolus
  For the initial 3000 IU (30 mg) bolus, using an enoxaparin sodium graduated pre-filled syringe, expel the excessive volume to retain only 3000 IU (30 mg) in the syringe. The 3000 IU (30 mg) 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
  An initial IV bolus injection of 3 000 IU followed by an SC injection of 100 IU/kg within 15 minutes, then every 12 hours (a maximum of 10000 IU for the 1st two SC doses).
  The 1st dose of enoxaparin sodium should be administered between 15 minutes before and 30 minutes after the start of thrombolytic therapy (whether fibrin-specific or not).
  The recommended duration of treatment is 8 days, or until the patient is discharged from hospital if the hospitalization is less than 8 days. Concomitant treatment: Aspirin therapy must be instituted as soon as possible after symptoms appear, and continued at a dose of between 75 mg and 325 mg daily for at least 30 days, unless otherwise indicated.
  For patients being managed with PCI, an additional IV bolus of 30 IU/kg (0.3 mg/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 (3 mg/mL).
  To obtain a 300 IU/mL (3 mg/mL) solution, using a 6000 IU (60 mg) 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 30 mL from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 6000 IU (60 mg) enoxaparin sodium pre-filled 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 IV 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 IV line after dilution is completed at a concentration of 300 IU (3 mg) /mL.

Weight [Kg]	Required dose 30 IU/kg (0.3 mg/kg) IU	[mg]	Volume to inject when diluted to a final concentration of 300 IU (3 mg) / mL [mL]
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 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 (see section Warnings & precautions).

- 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 2000 IU (20 mg) 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 (see also section Contraindications).
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 (0.75 mg/kg) twice daily or 100 IU/kg (1 mg/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.
Likewise, 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.

Instruction for Use: Pre-filled Syringe

Appropriate use of syringes is necessary to reduce the risk of pain and appearance of bruises at the injection site. Be careful to follow the instructions.

- Preparation of the injection site:
  Before performing the injection, wash your hands and dry them. Use a cotton ball to clean (without rubbing) the area chosen for the injection.
  Choose a different area of the stomach for each injection.
- Remove the protective cap from the needle.
  The appearance of a drop at the end of the needle is possible. In this case, remove the drop before injection by tapping on the body of the syringe (with the needle pointing downwards).
- Perform the injection
  The pre-filled syringe is ready for immediate use. The injection should be performed, preferably with the patient lying down, under the skin of the waist, whether on the right or on the left. The needle should be introduced perpendicularly and not tangentially, into the thickness of a skin fold pinched between the thumb and index finger of the operator. The fold should be held throughout the entire injection.
- Immediately throw away the syringe in the appropriate container
  Any unused medicinal product or waste material should be disposed of in accordance with local requirements

CONTRAINDICATIONS:

Enoxaparin sodium is contraindicated in patients with:

- Hypersensitivity to enoxaparin, heparin or its derivatives, including other low molecular weight heparins (LMWH) or to any of the excipients listed
- History of immune mediated heparin-induced thrombocytopenia (HIT), within the past 100 days or in the presence of circulating antibodies (see section Warnings and precautions)
- 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 anesthesia or loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24 hours (see section Warnings and precautions).

WARNING & PRECAUTIONS:

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 heparin-induced thrombocytopenia (>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 (see section Contraindications). 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 80 g/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. Should thrombocytopenia occur, it usually appears between the 5th and the 21st day following the beginning of enoxaparin sodium treatment.
The risk of HIT is higher in postoperative patients and mainly after cardiac surgery and in patients with cancer.
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.
If there are clinical symptoms suggestive of HIT (any new episode of arterial and/or venous thromboembolism, any painful skin lesion at the injection site, any allergic or anaphylactoid reactions on treatment), platelet count should be measured. Patients must be aware that these symptoms may occur and if so, that they should inform their primary care physician.
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 non-heparin anticoagulant alternative treatment.

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 (see section Interaction with other medicaments).

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 (see also section Contraindications).
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 4000 IU (40 mg) 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 (see section Pharmacokinetic). 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 [15-30 ml/min] dosage considerations are necessary because elimination of enoxaparin sodium is more prolonged (see section Dosage and administration).
Should the physician decide to administer anticoagulation in the context of epidural or spinal anaesthesia/analgesia 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. Instruct patients to report immediately if they experience any of the above signs or symptoms. 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 injections doses. It is important to achieve hemostasis at the puncture site after percutaneous coronary intervention (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 sign of bleeding or hematoma formation.

Acute infective endocarditis

Use of heparin is usually not recommended in patients with acute infective endocarditis due to the risk of cerebral hemorrhage. 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. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin sodium 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 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. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin sodium (100 IU/kg (1mg/kg) twice daily) 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 sodium for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism.

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 and dose reduction might be considered in patients older than 75 years treated for STEMI (see sections dosage and administration and pharmacokinetic).

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 (see sections Dosage and administration and Pharmacokinetic).
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.
In patients with severe renal impairment (creatinine clearance 15-30 ml/min), since exposure of enoxaparin sodium is significantly increased, a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges (see section Dosage and administration).
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.

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 (see section Pharmacokinetic).

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 section Pharmacokinetic).

Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/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 (see section Side effects), particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, taking medicinal products known to increase potassium (see section Interaction with other medicaments). 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.

PREGNANCY AND LACTATION:

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.
Animal studies have not shown any evidence of foetotoxicity or teratogenicity (see section Clinical studies). Animal data have shown that enoxaparin passage through the placenta is minimal.
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. Overall, the data suggest that there is no evidence for an increased risk of haemorrhage, thrombocytopenia or osteoporosis with respect to the risk observed in non-pregnant women, other than that observed in pregnant women with prosthetic heart valves (see section Warnings & precautions).
If an epidural anaesthesia is planned, it is recommended to withdraw enoxaparin sodium treatment before (see section Warnings & precautions).

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. Vaxcel Enoxaparin Sodium Injection can be used during breast-feeding.

Fertility

There are no clinical data for enoxaparin sodium in fertility. Animal studies did not show any effect on fertility (see section Clinical studies).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

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

INTERACTION WITH OTHER MEDICAMENTS:

Concomitant use not recommended

- Medicinal products affecting haemostasis (see section Warnings and precautions)
  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 (see section Dosage and administration).

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 (see sections Warnings and precautions and Side effects).

SIDE EFFECTS

Summary of the safety profile

Enoxaparin sodium has been evaluated in more than 15,000 patients who received enoxaparin sodium in clinical trials. These included 1,776 for prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1,169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of DVT with or without PE, 1,578 for treatment of unstable angina and non-Q-wave myocardial infarction and 10,176 for treatment of acute STEMI.

Enoxaparin sodium regimen administered during these clinical trials varies depending on indications. The enoxaparin sodium dose was 4000 IU (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 DVT with or without PE, patients receiving enoxaparin sodium were treated with either 100 IU/kg (1 mg/kg) SC dose

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every 12 hours or a 150 IU/kg (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 100 IU/kg (1 mg/kg) SC every 12 hours, and in the clinical study for treatment of acute STEMI enoxaparin sodium regimen was a 3,000 IU (30 mg) IV bolus followed by 100 IU/kg (1 mg/kg) SC every 12 hours.

In clinical studies, haemorrhages, thrombocytopenia and thrombocytosis were the most commonly reported reactions (see section Warnings and precautions and 'Description of selected adverse reactions' below).

The safety profile of enoxaparin for extended treatment of DVT and PE in patients with active cancer is similar to its safety profile for the treatment of DVT and PE.

Tabulated summary list of adverse reactions

Other 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); and very rare (< 1/10,000) or not known (cannot be estimated from available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
- Common: Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis
- Rare: Eosinophilia*
- Very rare: Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see section Warnings and precautions).

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 (see section Warnings and precautions).

Hepato-biliary disorders
- Very common: Hepatic enzyme increases (mainly transaminases > 3 times the upper limit of normal)
- Uncommon: Hepatocellular liver injury*
- Rare: Cholestatic liver injury*

Skin and subcutaneous tissue disorders
- Common: Urticaria, pruritus, erythema
- Uncommon: Bullous dermatitis
- Rare: Alopecia*
- Rare: 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.

Musculoskeletal, connective tissue and bone 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* (see sections Warnings and precautions and Interaction with other medicaments).

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, haemorrhagic complications were considered as major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by haemoglobin decrease ≥ 2 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 (see sections Warnings and precautions and Interaction with other medicaments).

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 the lymphatic system disorders	Very common: Haemorrhage[1] Rare: Retroperitoneal haemorrhage	Common: Haemorrhage[1]	Very common: Haemorrhage[1] Uncommon: Intracranial haemorrhage, Retroperitoneal haemorrhage	Common[2]: Haemorrhage	Common: Haemorrhage[1] Rare: Retroperitoneal haemorrhage	Common: Haemorrhage[1] Uncommon: Intracranial haemorrhage, Retroperitoneal haemorrhage

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

b: frequency based on retrospective study on a registry including 3526 patients (see section Clinical Studies).

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 the lymphatic system disorders	Very common: Thrombocytosis[1] Common: Thrombocytopenia	Uncommon: Thrombocytopenia	Very common: Thrombocytosis[1] Common: Thrombocytopenia	Unknown: Thrombocytopenia	Uncommon: Thrombocytopenia	Common: Thrombocytosis[1] Thrombocytopenia Very rare: Immuno-allergic thrombocytopenia[1]

β: Platelet increased >400 G/L

Pediatric population

The safety and efficacy of enoxaparin sodium in children have not been established (see section Dosage and administration).

SYMPTOMS AND TREATMENT OF 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:
- 1 mg protamine neutralizes the anticoagulant effect of 100 IU (1 mg) of enoxaparin sodium, if enoxaparin sodium was administered in the previous 8 hours.
  - An infusion of 0.5 mg protamine per 100 IU (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%) (see the prescribing information for protamine salts).

PHARMACODYNAMICS:

Pharmacotherapeutic group: Antithrombotic agent, ATC code: B01AB05.

Pharmacodynamic effects

Enoxaparin is a LMWH with a mean molecular weight of approximately 4,500 daltons, in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated. The drug substance is the sodium salt.

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), with a ratio of 3.6. These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti-thrombotic activities in humans.

Beyond its anti-Xa/IIa activity, further antithrombotic 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 antithrombotic effect of enoxaparin sodium.

When used as prophylactic treatment, enoxaparin sodium does not significantly affect the aPTT. When used as curative treatment, aPTT can be prolonged by 1.5-2.2 times the control time at peak activity.

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 SC administration and after single IV administration. The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by validated amidolytic methods.

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 2000 IU, 4000 IU, 100 IU/kg and 150 IU/kg (20 mg, 40 mg, 1 mg/kg and 1.5 mg/kg) doses, respectively.

A 3000 IU (30 mg) IV bolus immediately followed by 100 IU/kg (1 mg/kg) SC every 12 hours provided initial maximum anti-Xa activity level 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.

After repeated SC administration of 4000 IU (40 mg) once daily and 150 IU/kg (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. After repeated SC administration of the 100 IU/kg (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 maximum and trough anti-Xa activity levels of about 1.2 and 0.52 IU/mL, respectively.

Injection volume and dose concentration over the range 100-200 mg/mL does not affect pharmacokinetic parameters in healthy volunteers.

Enoxaparin sodium pharmacokinetics appears to be linear over the recommended dosage ranges.

Intra-patient and inter-patient variability is low. Following repeated SC administration, no accumulation takes place.

Plasma anti-IIa activity after SC administration is approximately ten-fold lower than anti-Xa activity. The mean maximum anti-IIa activity level is observed approximately 3 to 4 hours following SC injection and reaches 0.13 IU/mL and 0.19 IU/mL following repeated administration of 100 IU/kg (1 mg/kg) twice daily and 150 IU/kg (1.5 mg/kg) once daily, respectively.

Distribution

The volume of distribution of enoxaparin sodium anti-Xa activity is about 4.3 liters 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 (1.5 mg/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.

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 sections Dosage and administration and Warnings & precautions).

Hepatic impairment

In a study conducted in patients with advanced cirrhosis treated with enoxaparin sodium 4000 IU (40 mg) once daily, a decrease in maximum anti-Xa activity was associated with an increase in the severity of hepatic impairment (assessed by Child-Pugh categories). This decrease was mainly attributed to a decrease in ATIII level secondary to a reduced synthesis of ATIII in patients with hepatic impairment.

Renal impairment

A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed. However, since renal function is known to decline with age, elderly patients may show reduced elimination 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 SC 4000 IU (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 SC 4000 IU (40 mg) once daily doses (see section Dosage and administration).

Hemodialysis

Enoxaparin sodium pharmacokinetics appeared similar than control population, after a single 25 IU, 50 IU or 100 IU/kg (0.25, 0.50 or 1.0 mg/kg) IV dose however, AUC was two-fold higher than control.

Weight

After repeated SC 150 IU/kg (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/m²) compared to non-obese control subjects, while maximum plasma anti-Xa activity level is not increased. There is a lower weight-adjusted clearance in obese subjects with SC dosing.

When non-weight adjusted dosing was administered, it was found after a single-SC 4000 IU (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 section Warnings and precautions).

Pharmacokinetic Interaction

No pharmacokinetic interaction was observed between enoxaparin and thrombolytics when administered concomitantly.

CLINICAL STUDIES:

Clinical efficacy and safety

Biosimilarity between Vaxcel Enoxaparin Sodium Injection and Clexane

To support the demonstration of bioequivalence of Vaxcel Enoxaparin Sodium Injection to the reference medicinal product Clexane, a randomized, open-label, single-dose, two-period, crossover study to assess the pharmacokinetic and pharmacodynamic equivalence of Reference Product Clexane 10000 IU/1ml solution for injection in prefilled syringe and test formulation of Vaxcel Enoxaparin Sodium Injection 10000 IU/1ml solution for injection in prefilled syringe following subcutaneous administration in healthy subjects was conducted.

The pharmacokinetic and pharmacodynamic equivalence was based on the pharmacodynamic endpoints factor Xa inhibition (anti-Xa) and factor IIa inhibition (anti-IIa) as primary surrogate markers of bioavailability of each product.

Efficacy results:

Comparison of Standards for non-inferiority assessment for anti-IIa activity (N=55)

PK Variables	Reference (mean)	Test (mean)	Difference (Test-Reference)	CI 95% Difference	Δ, Non-inferiority margin
C_{max} (IU/mL)	0.2147	0.2061	-0.0086	[-0.0173; 0.000]	-0.0537
$AUEC_{0-t}$ (IU/mL*h)	1.3548	1.3153	-0.0395	[-0.1169; 0.0380]	-0.3387

Comparison of Standards for non-inferiority assessment for anti-Xa activity (N=56)

PK Variables	Reference (mean)	Test (mean)	Difference (Test-Reference)	CI 95% Difference	Δ, Non-inferiority margin
C_{max} (IU/mL)	0.7444	0.7943	0.0499	[0.0200; 0.0798]	-0.1117
$AUEC_{0-t}$ (IU/mL*h)	7.1793	7.7921	0.6127	[0.3514; 0.8741]	-1.0769

Study was conducted following a non-inferior approach, with pre-specified equivalence margins for anti-Xa and anti-IIa activities to fix the non-inferior margin, using a 95% confidence interval around the observed difference without log-transformation of the data while considering its lower side limit of non-inferiority testing. The margin of non-inferior was pre-specified at ±15% for anti-Xa activity and at ±25% for anti-IIa activity to counter for within-subject variability. To satisfy the condition of symmetrical equivalence limits on the log scale and considering the lower limit of the 95% two-side confidence interval above Δ, simple algebra brings the value 85.00% as (exp[-0.1625]), the value 75.00% as (exp[-0.2877]).

Anti-Xa activity: ln(0.85)= -0.1625

Anti-IIa activity: ln(0.75)= -0.2877

To keep the equivalence limits symmetric about 0, the following acceptance ranges was obtained: [85.00% - 117.65%] as (exp[±0.1625]) for Anti-Xa activity and [75.00% - 133.33%] as (exp[±0.2877]) for Anti-IIa activity, respectively.

Statistical analysis of primary pharmacodynamic parameters

Anti-Xa Activity					
PD Parameters	Test (p-value)	Reference (p-value)	Point estimate (%)	95% Confidence Interval (%)	Acceptance range of biosimilarity (%)
C_{max} (IU/mL)	0.1607	0.1294	107.46	103.28 – 111.81	85.00 – 117.65
$AUEC_{0-t}$ (h*IU/mL)	0.7976	0.7725	108.22	104.49 – 112.08	85.00 – 117.65
$AUEC_{0-inf}$ (h*IU/mL)	0.1754	0.3267	109.02	105.27 – 112.91	85.00 – 117.65

Anti-IIa Activity					
PD Parameters	Test (p-value)	Reference (p-value)	Point estimate (%)	95% Confidence Interval (%)	Acceptance range of biosimilarity (%)
C_{max} (IU/mL)	0.6404	0.6862	96.59	92.45 – 100.91	75.00 – 133.33
$AUEC_{0-t}$ (h*IU/mL)	0.4408	0.0792	96.74	90.71 – 103.17	75.00 – 133.33

The 95% CI of the ratio of the geometric least square means between Vaxcel Enoxaparin Sodium Injection and Clexane for C_{max}, $AUEC_{0-t}$ and $AUEC_{0-inf}$ of anti-Xa activity met the acceptance range of biosimilarity of 85.00% - 117.65%, while C_{max} and $AUEC_{0-t}$ of anti-IIa activity met the acceptance range of biosimilarity of 75.00% - 133.33%, thereby demonstrating pharmacodynamic biosimilarity of Vaxcel Enoxaparin Sodium Injection versus Clexane.

The bioequivalence between Vaxcel Enoxaparin Sodium Injection and Clexane was confirmed.

Clinical Studies done on the Reference Product (Clexane)

Prevention of venous thromboembolic disease associated with surgery
- Extended prophylaxis of VTE following orthopaedic surgery

  In a double-blind study of extended prophylaxis for patients undergoing hip replacement surgery, 179 patients with no venous thromboembolic disease initially treated, while hospitalized, with enoxaparin sodium 4000 IU (40 mg) SC, were randomized to post-discharge regimen of either enoxaparin sodium 4000 IU (40 mg) SC 2 days and a regimen of 30 mg SC to placebo (n=89) for 3 weeks. The incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo, no PE was reported. No major bleeding occurred.

  The efficacy data are provided in the table below

	Enoxaparin Sodium 4000 IU (40 mg) once a day SC n (%)	Placebo once a day SC n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Total VTE	6 (6.6)	18 (20.2)
• Total DVT (%)	6 (6.6)[*]	18 (20.2)
• Proximal DVT (%)	5 (5.6)[#]	7 (8.8)

*p value versus placebo =0.008
#p value versus placebo =0.537

  In a second double-blind study, 262 patients without VTE disease and undergoing hip replacement surgery initially treated, while hospitalized, with enoxaparin sodium 4 000 IU (40 mg) SC were randomized to a post-discharge regimen of either enoxaparin sodium 4 000 IU (40 mg) (n=131) once a day SC or to placebo (n=131) for 3 weeks. Similar to the first study the incidence of VTE during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo for both total VTE (enoxaparin sodium: 21 [16%] versus placebo: 45 [34.4%]; p=0.001) and proximal DVT (enoxaparin sodium: 8 [6.1%] versus placebo: 28 [21.4%]; p=<0.001). No difference in major bleeding was found between the enoxaparin sodium and the placebo group.
- Extended prophylaxis of DVT following cancer surgery

  A double-blind, multicenter trial, compared a four-week and a one-week regimen of enoxaparin sodium prophylaxis in the safety and efficacy in 332 patients undergoing elective surgery for abdominal or pelvic cancer. Patients received enoxaparin sodium (4,000 IU (40 mg) SC) daily for 6 to 10 days and were then randomly assigned to receive either enoxaparin sodium or placebo for another 21 days. Bilateral venography was performed between days 25 and 31, or sooner if symptoms of venous thromboembolism occurred. The patients were followed for three months. Enoxaparin sodium prophylaxis for four weeks after surgery for abdominal or pelvic cancer significantly reduced the incidence of venographically demonstrated thrombosis, as compared with enoxaparin sodium prophylaxis for one week. The rates of venous thromboembolism at the end of the double-blind phase were 12.0 % (n=20) in the placebo group and 4.8% (n=8) in the enoxaparin sodium group; p=0.02. This difference persisted at three months [13.8% vs. 5.5% (n=23 vs 9), p=0.01]. There were no differences in the rates of bleeding or other complications during the double-blind or follow-up periods.
- Prophylaxis of venous thromboembolic disease in medical patients with an acute illness expected to induce limitation of mobility

  In a double blind multicenter, parallel group study, enoxaparin sodium 2000 IU (20 mg) or 4000 IU (40 mg) once a day SC was compared to placebo in the prophylaxis of DVT in medical patients with severely restricted mobility during acute illness (defined as walking distance of <10 meters for ≤3 days). This study included patients with heart failure (NYHA Class III or IV); acute respiratory failure or complicated chronic respiratory insufficiency, and acute infection or acute rheumatic; if associated with at least one VTE risk factor (age ≥75 years, cancer, previous VTE, obesity, varicose veins, hormone therapy, and chronic heart or respiratory failure).

A total of 1,102 patients were enrolled in the study, and 1,073 patients were treated. Treatment continued for 6 to 14 days (median duration 7 days). When given at a dose of 4000 IU (40 mg) once a day SC, enoxaparin sodium significantly reduced the incidence of VTE as compared to placebo. The efficacy data are provided in the table below.

	Enoxaparin sodium 2000 IU (20 mg) once a day SC n (%)	Enoxaparin sodium 4000 IU (40 mg) once a day SC n (%)	Placebo n (%)
All Treated Medical Patients During Acute Illness	287 (100)	291(100)	288 (100)
Total VTE (%)	43 (15.0)	16 (5.5)[*]	43 (14.9)
• Proximal DVT (%)	43 (15.0)	16 (5.5)	40 (13.9)
	13 (4.5)	5 (1.7)	14 (4.9)

VTE = Venous thromboembolism events included DVT, PE, and death considered to be thromboembolic in origin

* p value versus placebo =0.0002

At approximately 3 months following enrolment, the incidence of VTE remained significantly lower in the enoxaparin sodium 4,000 IU (40 mg) treatment group versus the placebo treatment group.

The occurrence of total and major bleeding were respectively 8.6% and 1.1% in the placebo group, 11.7% and 0.3% in the enoxaparin sodium 2000 IU (20 mg) group and 12.6% and 1.7% in the enoxaparin sodium 4000 IU (40 mg) group.
- Treatment of deep vein thrombosis with or without pulmonary embolism

  In a multicenter, parallel group study, 900 patients with acute lower extremity DVT with or without PE were randomized to an inpatient (hospital) treatment of either (i) enoxaparin sodium 150 IU/kg (1.5 mg/kg) once a day SC, (ii) enoxaparin sodium 100 IU/kg (1 mg/kg) every 12 hours SC, or (iii) heparin IV bolus (5000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. All patients also received warfarin sodium dose adjusted according to prothrombin time to achieve an INR of 2.0 to 3.0), commencing within 72 hours of initiation of enoxaparin sodium or standard heparin therapy, and continuing for 90 days. Enoxaparin sodium or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both enoxaparin sodium regimens were equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism (DVT and/or PE). The efficacy data are provided in the table below.

	Enoxaparin sodium 150 IU/kg (1.5 mg/kg) once a day SC n (%)	Enoxaparin sodium 100 IU/kg (1 mg/kg) twice a day SC n (%)	Heparin aPTT Adjusted IV Therapy n (%)
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Total VTE (%)	13 (4.4)[*]	9 (2.9)[*]	12 (4.1)
• DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
• Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
• PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

VTE = venous thromboembolic event (DVT and/or PE)

*The 95% Confidence Intervals for the treatment differences for total VTE were:
- enoxaparin sodium once a day versus heparin (-3.0 to 3.5)
- enoxaparin sodium every 12 hours versus heparin (-4.2 to 1.7).

Major bleeding were respectively 1.7% in the enoxaparin sodium 150 IU/kg (1.5 mg/kg) once a day group, 1.3% in the enoxaparin sodium 100 IU/kg (1 mg/kg) twice a day group and 2.1% in the heparin group.
- Extended treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of its recurrence in patients with active cancer.

  In clinical trials with limited number of patients, reported rates of recurrent VTE in patients treated with enoxaparin given once or twice daily for 3 to 6 months appear comparable to those with warfarin.

  Effectiveness in real-life setting was assessed in a cohort of 4,451 patients with symptomatic VTE and active cancer from the multinational registry RIETE of patients with VTE and other thrombotic conditions. 3,526 patients received SC enoxaparin up to 6 months and 925 patients received tinzaparin or dalteparin SC. Among the 3,526 patients receiving enoxaparin treatment, 891 patients were treated with 1.5 mg/kg once daily as initial therapy and extended treatment up to 6 months (once daily alone), 1,854 patients received initial 1.0 mg/kg twice daily regimen and extended treatment up to 6 months (twice daily alone), and 687 patients received 1.0 mg/kg twice daily as initial treatment followed by 1.5 mg/kg once daily (twice daily-once daily) as the extended treatment up to 6 months. The mean and median duration of treatment until regimen change was 17 days and 8 days, respectively. There was no significant difference for VTE recurrence rate between the two treatments groups (see table), with enoxaparin meeting the prespecified criterion for non-inferiority of 1.5 (HR adjusted by relevant covariates 0.817, 95% CI: 0.499-1.336). There was no statistically significant difference between the two treatment groups with regards to the relative risks of major (fatal or non-fatal) bleeding and all-cause death (see table).

Table: Efficacy and safety outcomes in the RIETECAT study

Outcome	Enoxaparin n = 3526	Other LMWH n = 925	Adjusted Hazard Ratios enoxaparin / other LMWH [95% confidence interval]
VTE recurrence	70 (2.0%)	23 (2.5%)	0.817, [0.499 – 1.336]
Major bleeding	111 (3.1%)	18 (1.9%)	1.522, [0.899 – 2.577]
Non-major bleeding	87 (2.5%)	24 (2.6%)	0.881, [0.550 – 1.410]
Overall death	666 (18.9%)	157 (17.0%)	0.974, [0.813 – 1.165]

An overview of outcomes per treatment regimen used in the RIETECAT study among 6-month completers is provided below:

Table. 6-month outcomes in patients completing 6-month treatment, by different regimens

Outcome	Enoxaparin	Enoxaparin all regimens				EU-
N (%) (95% CI)	All regimens N = 1432	Enoxaparin BID N = 444	Enoxaparin BID N = 529	Enoxaparin BID to OD N = 406	Enoxaparin OD to BID N = 14	Enoxaparin more than one switch N = 39	Authorized LMWHs N = 428
Recurrence of VTE	70 (4.9%) (3.8% - 6.0%)	33 (7.4%) (5.2% - 9.9%)	22 (4.2%) (2.6% - 5.9%)	10 (2.5%) (0.9% - 4.0%)	1 (7.1%) (0% - 22.6%)	4 (10.3%) (0.3% - 20.2%)	23 (5.4%) (3.2% - 7.5%)
Major bleeding (fatal and non-fatal)	111 (7.8%) (6.4% - 9.1%)	31 (7.0%) (4.6% - 9.4%)	52 (9.8%) (7.3% - 12.4%)	21 (5.2%) (3.0% - 7.3%)	1 (7.1%) (0% - 22.6%)	6 (15.4%) (3.5% - 27.2%)	18 (4.2%) (2.3% - 6.1%)
Non-major bleedings of clinical significance	87 (6.1%) (4.9% - 7.3%)	26 (5.9%) (3.7% - 8.0%)	33 (6.2%) (4.2% - 8.3%)	23 (5.7%) (3.4% - 7.9%)	1 (7.1%) (0% - 22.6%)	4 (10.3%) (0.3% - 20.2%)	24 (5.6%) (3.4% - 7.8%)
All-cause death	666 (46.5%) (43.9% - 49.1%)	175 (39.4%) (34.9% - 43.9%)	323 (61.1%) (56.9% - 65.2%)	146 (36.0%) (31.3% - 40.8%)	6 (42.9%) (13.2% - 72.5%)	16 (41.0%) (24.9% - 57.2%)	157 (36.7%) (32.1% - 41.3%)
Fatal PE or fatal bleeding related death	48 (3.4%) (2.4% - 4.3%)	7 (1.6%) (0.4% - 2.7%)	35 (6.6%) (4.5% - 8.7%)	5 (1.2%) (0.2% - 2.3%)	0 (0%) -	2 (5.1%) (0% - 7.8%)	11 (2.6%) (1.1% - 4.1%)

*All data with 95% CI

- Treatment of unstable angina and non ST elevation 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 acetylsalicylic acid (100 to 325 mg once daily), either SC enoxaparin sodium 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on 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. In comparison with heparin, enoxaparin sodium significantly reduced the combined incidence of angina pectoris, myocardial infarction and death, with a decrease of 19.8 to 16.6% (relative risk reduction of 16.2%) on day 14. This reduction in the combined incidence was maintained after 30 days (from 23.3 to 19.8%; relative risk reduction of 15%).

  There were no significant differences in major haemorrhages, although a haemorrhage at the site of the SC injection was more frequent.
- Treatment of acute ST-segment elevation myocardial infarction

  In a large multicenter study, 20,479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium in a single 3,000 IU (30 mg) IV bolus plus a 100 IU/kg (1 mg/kg) SC dose followed by an SC injection of 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT for 48 hours. All patients were also treated with acetylsalicylic acid for a minimum of 30 days. The enoxaparin sodium 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 sodium were given until hospital discharge or for a maximum of eight days (whichever came first).

  4,716 patients underwent percutaneous coronary intervention receiving antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin sodium, the PCI was to be performed on enoxaparin sodium (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 30 IU/ kg (0.3 mg/kg) enoxaparin sodium, 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 sodium 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 sodium, 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 sodium 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 sodium, 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 intracranial haemorrhage (a measure of net clinical benefit) was significantly lower (p<0.0001) in the enoxaparin sodium group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favour of treatment with enoxaparin sodium.

The incidence of major bleeding at 30 days was significantly higher (p<0.0001) in the enoxaparin sodium group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin sodium group (0.5%) versus the heparin group (0.1%), while the incidence of intracranial haemorrhage was similar in both groups (0.8% with enoxaparin sodium versus 0.7% with heparin).

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

  Based on literature data the use of enoxaparin sodium 4,000 IU (40 mg) in cirrhotic patients (Child-Pugh class B-C) appears to be safe and effective in preventing portal vein thrombosis. It should be noted that the literature studies may have limitations. Caution should be used in patients with hepatic impairment as these patients have an increased potential for bleeding (see section Warnings and precautions) and no formal dose finding studies have been performed in cirrhotic patients (Child Pugh class A, B nor C).

PRECLINICAL SAFETY DATA:

Besides the anticoagulant effects of enoxaparin sodium, there was no evidence of adverse effects at 15 mg/kg/day in the 13-week SC toxicity studies both in rats and dogs and at 10 mg/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 the *in vivo* rat bone marrow chromosomal aberration test.

Studies conducted in pregnant rats and rabbits at SC doses of enoxaparin sodium up to 30 mg/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 20 mg/kg/day.

STORAGE:

Do not store above 25°C.

Do not freeze.

This medicinal product is for single use only. Discard any unused product.

SHELF LIFE:

Do not use after the expiry date indicated on the outer packaging.

KEEP OUT OF REACH OF CHILDREN

JAUHI DARI KANAK-KANAK

PACK QUANTITIES:

Boxes of 2 pre-filled syringes for:

Vaxcel Enoxaparin Sodium 2000 IU (20mg)/0.2ml Injection, Vaxcel Enoxaparin Sodium 4000 IU (40mg)/0.4ml Injection, Vaxcel Enoxaparin Sodium 6000 IU (60mg)/0.6ml Injection.

Vaxcel Enoxaparin Sodium 2000 IU (20mg)/0.2ml Injection Prefilled Syringe : MAL24066008AZ

Vaxcel Enoxaparin Sodium 4000 IU (40mg)/0.4ml Injection Prefilled Syringe : MAL24066009AZ

Vaxcel Enoxaparin Sodium 6000 IU (60mg)/0.6ml Injection Prefilled Syringe : MAL24066010AZ

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