ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

6 000 IU (60 mg)/0.6 mL

Each pre-filled syringe contains enoxaparin sodium 6 000 IU anti-Xa activity (equivalent to 60 mg) in 0.6 mL water for injection.

For the full list of excipients, see section 6.1.

Enoxaparin sodium is a biological substance obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringes.

Clear, colorless to yellowish solution, pH value 5.5-7.5.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Lovenox is indicated in adults for:

- Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular 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.
- Prevention of thrombus formation in extra corporeal circulation during hemodialysis.
- 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 (20 mg) once daily by subcutaneous (SC) injection. Preoperative initiation (2 hours before surgery) of enoxaparin sodium 2 000 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). Prophylaxis 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 4 000 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 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 (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 thromboembolic 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 4.2).

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 3 000 IU (30 mg) plus a 100 IU/kg (1 mg/kg) SC dose followed by 100 IU/kg (1 mg/kg) administered SC every 12 hours (maximum 10 000 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.

Pediatric population

The safety and efficacy of enoxaparin sodium in pediatric 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 (see below “renal impairment” and section 4.4).

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 4.4.

Hepatic impairment

Limited data are available in patients with hepatic impairment (see sections 5.1 and 5.2) and caution should be used in these patients (see section 4.4).

Renal impairment (see sections 4.4 and 5.2)

- 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 hemodialysis.

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 (20 mg) SC once daily
Treatment of DVT and PE	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 3 000 IU (30 mg) 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 hemodialysis indication.

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

Method of administration

Lovenox should not be administered by the intramuscular route.

For the prophylaxis of venous thrombo-embolic disease following surgery, treatment of DVT and PE, 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 hemodialysis, 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 multi-dose 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 (30 mg) bolus
    For the initial 3 000 IU (30 mg) bolus, using an enoxaparin sodium graduated pre-filled syringe, expel the excessive volume to retain only 3 000 IU (30 mg) in the syringe. The 3 000 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

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 6 000 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 6 000 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	Required dose 30 IU/kg (0.3 mg/kg)	Volume to inject when diluted to a final concentration of 300 IU (3 mg)/mL	
[Kg]	IU	[mg]	[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 hemodialysis.

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 anesthesia or lumbar puncture

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, careful neurological monitoring is recommended due to the risk of neuraxial hematomas (see section 4.4).

- *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 (20 mg) is not compatible with neuraxial anesthesia.
- *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 4.3).
  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.

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 listed in section 6.1;
- History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (see also section 4.4);
- Active clinically significant bleeding and conditions with a high risk of hemorrhage, including recent hemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities;
- Spinal or epidural anesthesia or loco-regional anesthesia when enoxaparin sodium is used for treatment in the previous 24 hours (see section 4.4).

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 (see section 4.3). 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

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.

Hemorrhage

As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the hemorrhage should be investigated and appropriate treatment instituted.

Enoxaparin sodium, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as:

- impaired hemostasis,
- history of peptic ulcer,
- recent ischemic stroke,
- severe arterial hypertension,
- recent diabetic retinopathy,
- neuro- or ophthalmologic surgery,
- concomitant use of medications affecting hemostasis (see section 4.5).

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 anesthesia or lumbar puncture

Spinal/epidural anesthesia or lumbar puncture must not be performed within 24 hours of administration of enoxaparin sodium at therapeutic doses (see also section 4.3).

There have been cases of neuraxial hematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anesthesia or spinal puncture procedures resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 4 000 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 hemostasis 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 anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium (see section 5.2).

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/minute], additional considerations are necessary because elimination of enoxaparin sodium is more prolonged (see section 4.2).

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/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 injection doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation.

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 fetal 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 (1 mg/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 4.2 and 5.2).

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 4.2 and 5.2).

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 hemodialysis.

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 4.2).

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 5.2).

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 5.2).

Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m^2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

Hyperkalemia

Heparins can suppress adrenal secretion of aldosterone leading to hyperkalemia (see section 4.8), 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 4.5). 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.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

- Medicinal products affecting hemostasis (see section 4.4)
  It is recommended that some agents which affect hemostasis 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 4.2).

Concomitant use with caution

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

- Other medicinal products affecting hemostasis 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 4.4 and 4.8).

4.6. Fertility, 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 fetotoxicity or teratogenicity (see section 5.3). 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 hemorrhagic risk. Overall, the data suggest that there is no evidence for an increased risk of hemorrhage, 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 4.4).

If an epidural anesthesia is planned, it is recommended to withdraw enoxaparin sodium treatment before (see section 4.4).

Breastfeeding

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. **Lovenox** can be used during breastfeeding.

Fertility

There are no clinical data for enoxaparin sodium in fertility. Animal studies did not show any effect on fertility (see section 5.3).

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

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 orthopedic 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 4 000 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 a 100 IU/kg (1 mg/kg) SC dose 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, hemorrhages, thrombocytopenia and thrombocytosis were the most commonly reported reactions (see section 4.4 and 'Description of selected adverse reactions' below).

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 (≥1/1 000 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: Hemorrhage, hemorrhagic anemia*, thrombocytopenia, thrombocytosis
- Rare: Eosinophilia*, cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischemia (see section 4.4).

Immune system disorders

- Common: Allergic reaction
- Rare: Anaphylactic/Anaphylactoid reactions including shock*

Nervous system disorders

- Common: Headache*

Vascular disorders

- Rare: Spinal hematoma* (or neuraxial hematoma). These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section 4.4).

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 tissue 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.

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 hematoma, injection site pain, other injection site reaction (such as edema, hemorrhage, hypersensitivity, inflammation, mass, pain, or reaction)
- Uncommon: Local irritation, skin necrosis at injection site

Investigations

- Rare: Hyperkalemia* (see sections 4.4 and 4.5).

Description of selected adverse reactions

Hemorrhages

These included major hemorrhages, reported at most in 4.2% of the patients (surgical patients). Some of these cases have been fatal. In surgical patients, hemorrhage complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major.

As with other anticoagulants, hemorrhage 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 hemostasis (see sections 4.4 and 4.5).

System Organ Class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
Blood and lymphatic system disorders	*Very common*: **Hemorrhage**[α] *Rare:* **Retroperitoneal hemorrhage**	*Common:* **Hemorrhage**[α]	*Very common:* **Hemorrhage**[α] *Uncommon:* **Intracranial hemorrhage, Retroperitoneal hemorrhage**	*Common:* **Hemorrhage**[α] *Rare:* **Retroperitoneal hemorrhage**	*Common:* **Hemorrhage**[α] *Uncommon:* **Intracranial hemorrhage, Retroperitoneal hemorrhage**

[α]: such as hematoma, ecchymosis other than at injection site, wound hematoma, hematuria, epistaxis and gastro-intestinal hemorrhage.

Thrombocytopenia and thrombocytosis

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

[β]: Platelet increased >400 G/L

Pediatric population

The safety and efficacy of enoxaparin sodium in children have not been established (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the French national reporting system, i.e. *Agence nationale de Sécurité du Médicament et des Produits de Santé* (ANSM) under "*réseau des Centres de Pharmacovigilance*" (Network of Pharmacovigilance centers) – Website: www.ansm.sante.fr.

4.9. Overdose

Signs and symptoms

Accidental overdose with enoxaparin sodium after IV, extracorporeal or SC administration may lead to hemorrhagic 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).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent, heparin group, 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.

Clinical efficacy and safety

Prevention of venous thromboembolic disease associated with surgery

Extended prophylaxis of VTE following orthopedic 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 4 000 IU (40 mg) SC, were randomized to a post-discharge regimen of either enoxaparin sodium 4 000 IU (40 mg) (n=90) once a day SC or 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 4 000 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 terms of 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 2 000 IU (20 mg) or 4 000 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 4 000 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 2 000 IU (20 mg) once a day SC n (%)	**Enoxaparin sodium 4 000 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)
• Total DVT (%)	43 (15.0)	16 (5.5)	40 (13.9)
• Proximal DVT (%)	13 (4.5)	5 (1.7)	14 (4.9)
VTE = Venous thromboembolic events which 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 2 000 IU (20 mg) group and 12.6% and 1.7% in the enoxaparin sodium 4 000 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 (5 000 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.

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 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 hemorrhages, although a hemorrhage 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 (PCI) 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 hemorrhage (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 favor 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 hemorrhage 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 4.4) and no formal dose finding studies have been performed in cirrhotic patients (Child Pugh class A, B nor C).

5.2. Pharmacokinetic properties

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 2 000 IU, 4 000 IU, 100 IU/kg and 150 IU/kg (20 mg, 40 mg, 1 mg/kg and 1.5 mg/kg) doses, respectively.

A 3 000 IU (30 mg) IV bolus immediately followed by a 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 4 000 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 section 4.4).

Hepatic impairment

In a study conducted in patients with advanced cirrhosis treated with enoxaparin sodium 4 000 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, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-50 mL/min) renal impairment after repeated SC 4 000 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 4 000 IU (40 mg) once daily doses (see sections 4.2 and 4.4).

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/m^2) 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 4 000 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 4.4).

Pharmacokinetic interactions

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

5.3. 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 *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 30 mg/kg/day did not reveal any evidence of teratogenic effects or fetotoxicity. 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

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 medicines, except those mentioned in section 4.2.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25 °C. Do not freeze.

6.5. Nature and contents of container

Solution for injection in (type I glass) pre-filled syringes fitted with a (chlorobutyl and bromobutyl) rubber stopper and an injection needle (with an ERIS™ or PREVENTIS™ automatic safety system or without an automatic safety system).

Boxes of 2, 5, 6, 10, 12, 20, 24, 30, 50 or 100 pre-filled syringes, and multi-packs of 3 x 10 and 9 x 10 pre-filled syringes.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Pre-filled syringes are ready for use. See section 4.2 for the method of administration.

Use only clear, colorless to yellowish solution.

Pre-filled syringes are supplied with or without an automatic safety system. The instructions for use are provided in the package leaflet.

Each syringe is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Sanofi-Aventis France
82, avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORIZATION NUMBER(S)

- 34009 336 057 8 0: 0.6 mL solution for injection in pre-filled (glass) syringes – box of 2.
- 34009 336 058 4 1: 0.6 mL solution for injection in pre-filled (glass) syringes – box of 10.
- 34009 364 690 3 7: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 2.
- 34009 301 539 8 7: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 5.
- 34009 301 539 9 4: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 6.
- 34009 364 692 6 6: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 10.
- 34009 301 540 0 7: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 12.
- 34009 301 540 1 4: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 20.
- 34009 301 540 2 1: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 24.
- 34009 301 540 3 8: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 30.

- 34009 550 577 0 3: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 50.
- 34009 550 577 1 0: 0.6 mL solution for injection in pre-filled (glass) syringes with ERIS™ safety system – box of 100.
- 34009 300 142 4 0: 0.6 mL solution for injection in pre-filled (glass) syringes with PREVENTIS™ safety system – box of 2.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

[To be completed subsequently by the Marketing Authorization holder]

10. DATE OF REVISION OF THE TEXT

[To be completed subsequently by the Marketing Authorization holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

A.1. Name and address of the manufacturer(s) of the biological active substance(s)

VLG CHEM
35, avenue Jean Jaurès
92390 Villeneuve la Garenne
France

or

Aventis Pharma Manufacturing PTE LTD
61, Gul Circle
Singapore 629585

A.2. Name and address of the manufacturer(s) responsible for batch release

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

Sanofi Winthrop Industrie
Boulevard industriel,
Zone industrielle
76580 Le Trait
France

or

Sanofi Winthrop Industrie
180, rue Jean Jaurès
94700 Maisons-Alfort
France

or

Chinoin Pharmaceutical and Chemical Works Private Co. Ltd
Csanyikvolgy Site
Miskolc, Csanyikvolgy H 3510
Hungary

or

Sanofi-Aventis Private Co. Ltd
Budapest Logistics and Distribution Platform
Bdg. DC5, Campona Utcal
Budapest, 1225
Hungary

or

Sanofi-Aventis GmbH
Saturn Tower, Leonard Bernstein Strasse 10
1220 Vienna
Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

List I.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

Not applicable.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORIZATION MEASURES FOR THE MARKETING AUTHORIZATION UNDER EXCEPTIONAL CIRCUMSTANCES

Not applicable.

F. QUALITATIVE AND QUANTITATIVE COMPOSITION IN EXCIPIENTS

Water for injection..... q. s. 0.6 mL

ANNEX IIIA

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

NATURE/TYPE OUTER PACKAGING OR IMMEDIATE PACKAGING

Outer packaging: pre-filled syringes.

Multipacks: inner packaging and outer packaging.

1. NAME OF THE MEDICINAL PRODUCT

Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

Enoxaparin sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe (0.6 mL) contains 6 000 IU (60 mg) enoxaparin sodium.

3. LIST OF EXCIPIENTS

Water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Outer packaging: pre-filled syringes

Solution for injection in pre-filled syringes.

Box of 2, 5, 6, 10, 12, 20, 24, 30, 50 or 100 pre-filled syringes with or without an automatic safety system.

Multipacks

Inner packaging

10 pre-filled syringes. Multipack item; cannot be sold separately.

10 pre-filled syringes with safety system. Multipack item; cannot be sold separately.

Outer packaging

30 (3 boxes of 10) pre-filled syringes.

30 (3 boxes of 10) pre-filled syringes with safety system.

90 (9 boxes of 10) pre-filled syringes.

90 (9 boxes of 10) pre-filled syringes with safety system.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous, intravenous use.

Extracorporeal use (in the dialysis circuit).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder
Sanofi-Aventis France
82, avenue Raspail
94250 Gentilly
France

Operator
Sanofi-Aventis France
82, avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORIZATION NUMBER(S)

Marketing Authorization No.

13. BATCH NUMBER

Batch {number}.

14. GENERAL CLASSIFICATION FOR SUPPLY

List I.

15. INSTRUCTIONS ON USE

Not applicable.

16. INFORMATION IN BRAILLE

[The Decision of May 7, 2008, in application of Article R.5121-138 of the French Public Health Code, published in the Official Journal of the Republic of France of May 22, 2008 must be complied with.]

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer packaging pre-filled syringes

2D barcode carrying the unique identifier included.

Multipack

Inner packaging

Not applicable.

Outer packaging

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Outer packaging Pre-filled syringes

PC: {number}

SN: {number}

Multipack

Inner packaging

Not applicable.

Outer packaging

PC: {number}

SN: {number}

PICTOGRAM TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

[Pictogram relative to teratogenic or fetotoxic effects]

If applicable, the pictogram mentioned in section III of Article R. 5121-139 of the French Public Health Code (teratogenic or fetotoxic effects) must be affixed in accordance with the application decree provided for in the same article.

[Pictogram relative to effects on the ability to drive]

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

NATURE/TYPE BLISTERS/STRIPS

White blister

Transparent blister

1. NAME OF THE MEDICINAL PRODUCT

White blister

Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

Enoxaparin sodium

Transparent blister

Not applicable.

2. NAME OF THE MARKETING AUTHORIZATION HOLDER

White blister

Sanofi-Aventis France

Transparent blister

Not applicable.

3. EXPIRY DATE

White blister

EXP {MM/YYYY}

Transparent blister

Not applicable.

4. BATCH NUMBER

White blister

Batch {number}

Transparent blister

Not applicable.

5. OTHER

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

NATURE/TYPE SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

Enoxaparin[1]

2. METHOD OF ADMINISTRATION

SC/IV

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Not applicable.

6. OTHER

Not applicable.

[1] Translator's note: Original document in French should read "Enoxaparin sodium".

ANNEX IIIB

PACKAGE LEAFLET: INFORMATION FOR THE USER

Name of the medicinal product

Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

Enoxaparin sodium

Text box

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT LOVENOX 6 000 IU (60 MG)/0.6 ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGES IS AND WHAT IT IS USED FOR

Pharmacotherapeutic group: Antithrombotic agent, heparin group, ATC code: B01AB05

Lovenox contains an active substance called enoxaparin sodium. It belongs to a group of medicines called “low molecular weight heparins” or LMWHs.

How Lovenox works

Lovenox works in two ways:

1) Stopping existing blood clots from getting any bigger. This helps your body to break them down and stops them from causing you harm.

2) Stopping new blood clots from forming in your blood.

Why Lovenox is used

Lovenox can be used to:

- Treat blood clots that are in your blood
- Stop blood clots from forming in your blood in the following situations:
  - Before and after an operation
  - When you have a short-term illness and will not be able to move around for some time
- Stop blood clots from forming when you have unstable angina (a condition when not enough blood gets to your heart) or after a heart attack
- Stop blood clots from forming in the tubes of your dialysis machine (used for people with severe kidney problems).

2. WHAT YOU NEED TO KNOW BEFORE YOU USE LOVENOX 6 000 IU (60 MG)/0.6 ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGES

Do not use Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes if:

- you are allergic to:
  - enoxaparin sodium or any of the other ingredients of this medicine (listed in section 6)
  - heparin or other low molecular weight heparins such as nadroparin, tinzaparin or dalteparin.

  Signs of an allergic reaction include: rash, breathing or swallowing problems, swelling of your face, lips, mouth, throat or eyes.
- you have had a reaction to heparin that caused a severe drop in the number of your clotting cells (platelets) within the last 100 days
- you have antibodies against enoxaparin in your blood
- you are bleeding heavily or have a condition with a high risk of bleeding such as:
  - stomach ulcer, recent surgery of the brain or eyes or a recent bleeding stroke.
- you are using **Lovenox** to treat blood clots and within 24 hours you are going to have:
  - a spinal or lumbar puncture
  - surgery with spinal or epidural anesthesia.

Do not use **Lovenox** if any of the situations above applies to you. If you are not sure, talk to your doctor or pharmacist before using **Lovenox**.

Warnings and precautions

Lovenox should not be used interchangeably with other low molecular weight heparins such as nadroparin, tinzaparin or dalteparin. This is because they are not exactly the same and do not have the same activity and instructions for use.

Talk to your doctor or pharmacist before using **Lovenox** if:

- you have ever had a reaction to heparin that caused a severe drop in the number of your clotting cells (platelets)
- you have had a heart valve fitted
- you have endocarditis (an infection of the inner lining of the heart)
- you have a history of gastric ulcer
- you have had a recent stroke
- you have high blood pressure
- you have diabetes or problems with blood vessels in the eye caused by diabetes (called diabetic retinopathy)
- you have had an operation recently on your eyes or brain
- you are elderly (over 65 years old) and especially if you are over 75 years old
- you have kidney problems
- you have liver problems
- you are underweight or overweight
- you have high levels of potassium in your blood (this may be checked with a blood test)
- you are currently using medicines which increase the risk of bleeding (see section 2 below – Other medicines and **Lovenox** 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes)
- you have any problems with your spine or you have had spinal surgery.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using **Lovenox**.

Tests and checks

You may have a blood test before you start using this medicine and at intervals while you are using it; this is to check the level of the clotting cells (platelets) and potassium in your blood.

Children and adolescents

The safety and efficacy of **Lovenox** have not been evaluated in children or adolescents.

Other medicines and Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

Tell your doctor or pharmacist if you are taking or might take any other medicines.

- warfarin – used for thinning the blood
- aspirin (also known as acetylsalicylic acid or ASA), clopidogrel or other medicines used to stop blood clots from forming (see section 3, “Changing anticoagulant medicines”)
- dextran injection – used as a blood replacer
- ibuprofen, diclofenac, ketorolac or other medicines known as non-steroidal anti-inflammatory agents which are used to treat pain and swelling in arthritis and other conditions
- prednisolone, dexamethasone or other medicines used to treat asthma, rheumatoid arthritis and other conditions
- medicines which increase potassium levels in your blood such as potassium salts, water pills and some medicines for heart problems.

Operations and Anesthetics

If you are going to have a spinal or lumbar puncture or an operation where an epidural or spinal anesthetic is used, tell you doctor that you are using **Lovenox**.

Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes with food and drink

Not applicable.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant and have a mechanical heart valve, you may be at an increased risk of developing blood clots. Your doctor should discuss this with you.

If you are breast-feeding or plan to breast-feed, you should ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Lovenox does not affect the ability to drive and operate machinery.

It is advised that the trade name and batch number of the product you are using are recorded by your healthcare professional.

Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes contains

Not applicable.

3. HOW TO USE LOVENOX 6 000 IU (60 MG)/0.6 ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGES

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Having this medicine

- Your doctor or nurse will normally give you **Lovenox**. This is because it needs to be given as an injection.
- **Lovenox** is usually given by injection underneath the skin (subcutaneous).
- **Lovenox** can be given by injection into your vein (intravenous) after certain types of heart attack or operation.
- **Lovenox** can be added to the tube leaving the body (arterial line) at the start of the dialysis session.
- Do not inject **Lovenox** into a muscle.

How much will be given to you

- Your doctor will decide how much **Lovenox** to give you. The amount will depend on the reason it is being used.
- If you have problems with your kidneys you may be given a smaller amount of **Lovenox**.

1. Treating blood clots that are in your blood

- The usual dose is 150 IU (1.5 mg) for every kilogram of your weight each day or 100 IU (1 mg) for every kilogram of your weight twice a day.
- Your doctor will decide how long you should receive **Lovenox**.

2. Stopping blood clots from forming in your blood during operations or periods of limited mobility due to an illness

- The dose will depend on how likely you are to develop a clot. You will be given 2 000 IU (20 mg) or 4 000 IU (40 mg) of **Lovenox** each day.
- If you are going to have an operation your first injection will usually be given 2 hours or 12 hours before your operation.
- If you have restricted mobility due to illness, you will normally be given 4 000 IU (40 mg) of **Lovenox** each day.
- Your doctor will decide how long you should receive **Lovenox**.

3. Treating and preventing blood clots if you have unstable angina or after a heart attack

Lovenox can be used for two different types of heart attack. The amount of **Lovenox** given to you will depend on your age and the kind of heart attack you have had.

NSTEMI (Non-ST segment Elevation Myocardial Infarction) type of heart attack:

- The usual dose is 100 IU (1 mg) for every kilogram of weight every 12 hours.
- Your doctor will normally ask you to take aspirin (acetylsalicylic acid) as well.
- Your doctor will decide how long you should receive **Lovenox**.

STEMI (ST segment Elevation Myocardial Infarction) type of heart attack if you are under 75 years old:

- An initial dose of 3 000 IU (30 mg) of **Lovenox** will be given as injection into your vein.
- At the same time you will also be given **Lovenox** as an injection underneath your skin (subcutaneous injection). The usual dose is 100 IU (1 mg) for every kilogram of your weight, every 12 hours.
- Your doctor will normally ask you to take aspirin (acetylsalicylic acid) as well.
- Your doctor will decide how long you should receive **Lovenox**.

STEMI (ST segment Elevation Myocardial Infarction) type of heart attack if you are 75 years old or older:

- The usual dose is 75 IU (0.75 mg) for every kilogram of your weight, every 12 hours.
- The maximum amount of **Lovenox** given for the first two injections is 7 500 IU (75 mg).
- Your doctor will decide how long you should receive **Lovenox**.

For patients that have an operation called percutaneous coronary intervention (PCI):

Depending on when you were last given **Lovenox**, your doctor may decide to give an additional dose of **Lovenox** before a PCI operation. This is by injection into your vein.

4. Stopping blood clots from forming in the tubes of your dialysis machine

- The usual dose is 100 IU (1 mg) for every kilogram of your weight.
- **Lovenox** is added to the tube leaving the body (arterial line) at the start of the dialysis session. This amount is usually enough for a 4-hour session. However, your doctor may give you a further dose of 50 IU to 100 IU (0.5 to 1 mg) for every kilogram of your weight, if necessary.

Self-injecting Lovenox

If you are able to self-inject **Lovenox**, your doctor or nurse will show you how to do it. Do not try to self-inject if you have not been trained how to. If you are not sure what to do, talk to your doctor or nurse immediately. Injecting correctly under the skin (by “subcutaneous injection”) will help reduce pain and bruising at the injection site.

Before self-injecting Lovenox

- Gather together all the items you need: syringe, alcohol swab or soap and water, a container for sharp objects.
- Check the expiry date of the medicine. Do not use it if the date has passed.
- Make sure that the syringe is not damaged and that the medicine inside is a clear solution. Otherwise, use another syringe.
- Make sure that you know how much you are going to inject.
- Check your stomach to see if the last injection caused any redness, change in skin color, swelling, oozing or is still painful. If so, talk to your doctor or nurse.

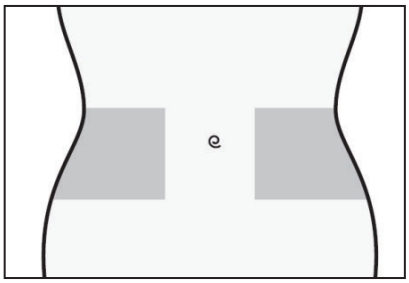
How to self-inject Lovenox 6 000 IU (60 mg)/0.6 mL

(Instructions for syringes without a safety system)

Preparing the injection site

1. Choose an area on the right or left side of your stomach, at least 5 centimeters away from your belly button and out towards your sides.

- Do not inject within 5 cm of your belly button or near scars or bruises.
- Alternate the injection site between the right and left sides of your stomach, depending on the area you last injected.



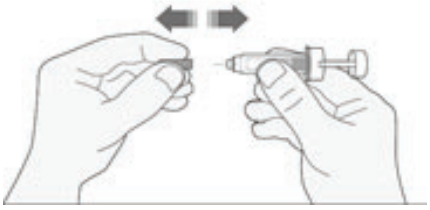
2. Wash your hands. Clean (do not rub) the area that you will inject with an alcohol swab or soap and water.

3. Sit or lie in a comfortable position so you are relaxed. Make sure you can see the place you are going to inject. A lounge chair, recliner, or bed propped up with pillows is ideal.

Selecting your dose

1. Carefully pull off the needle cap from the syringe. Throw away the cap.

- Do not press on the plunger to get rid of air bubbles before self-injecting, as you might lose some of the medicine.
- Once you have removed the cap, do not allow the needle to touch anything. This is to make sure the needle stays clean (sterile).



2. When the amount of medicine in the syringe already matches your prescribed dose, there is no need to adjust the dose. You are now ready to inject.

3. When the dose depends on your body weight, you may need to adjust the dose in the syringe to match the prescribed dose. In that case, you can get rid of any excess medicine by holding the syringe pointing down (to keep the air bubble in the syringe) and ejecting the extra amount into a container.

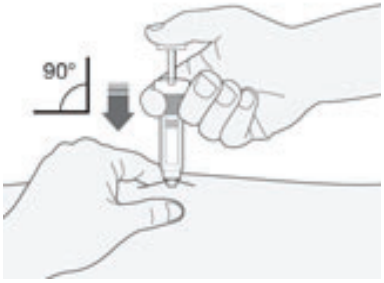
4. A drop may appear at the tip of the needle. If this occurs, remove the drop before injecting by tapping on the syringe with the needle pointing down. You are now ready to inject.

Injecting

1. Hold the syringe in the hand you write with (like a pencil). With your other hand, gently pinch the cleaned area of your stomach between your forefinger and thumb to make a fold in the skin.

- Make sure you hold the skin fold throughout the injection.

2. Hold the syringe so that the needle is pointing straight down (at a 90° angle to your skin). Insert the full length of the needle into the skin fold.



3. Press down on the plunger with your thumb. This will inject the medicine into the fatty tissue of your stomach. Complete the injection using all of the medicine in the syringe.

4. Remove the needle from the injection site by pulling it straight out. Do not point the needle towards yourself or others. You can now let go of the skin fold.

When you have finished

1. To avoid bruising, do not rub the injection site after you have self-injected.

2. Throw the used syringe away in the container for sharp objects. Close the container lid tightly and place it out of the reach of children. When the container is full, dispose of it as your doctor or pharmacist has instructed.

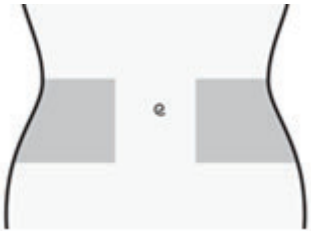
Any unused medicine or waste material should be disposed of in accordance with local requirements.

(Instructions for syringes with the ERIS™ automatic safety system)

Preparing the injection site

1. Choose an area on the right or left side of your stomach, at least 5 centimeters away from your belly button and out towards your sides.

- Do not inject within 5 cm of your belly button or near scars or bruises.
- Alternate the injection site between the right and left sides of your stomach, depending on the area you last injected.



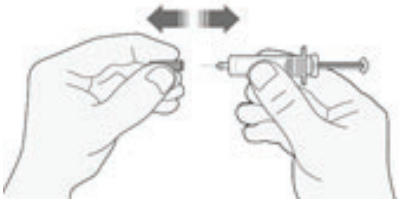
2. Wash your hands. Clean (do not rub) the area that you will inject with an alcohol swab or soap and water.

3. Sit or lie in a comfortable position so you are relaxed. Make sure you can see the place you are going to inject. A lounge chair, recliner, or bed propped up with pillows is ideal.

Selecting your dose

1. Carefully pull off the needle cap from the syringe. Throw away the cap.

- Do not press on the plunger to get rid of air bubbles before self-injecting, as you might lose some of the medicine.
- Once you have removed the cap, do not allow the needle to touch anything. This is to make sure the needle stays clean (sterile).



2. When the amount of medicine in the syringe already matches your prescribed dose, there is no need to adjust the dose. You are now ready to inject.

3. When the dose depends on your body weight, you may need to adjust the dose in the syringe to match the prescribed dose. In that case, you can get rid of any excess medicine by holding the syringe pointing down (to keep the air bubble in the syringe) and ejecting the extra amount into a container.

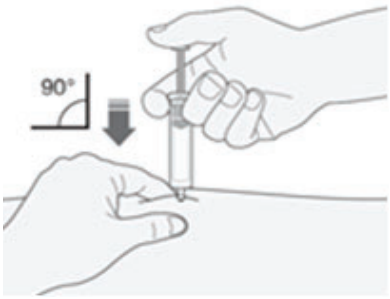
4. A drop may appear at the tip of the needle. If this occurs, remove the drop before injecting by tapping on the syringe with the needle pointing down. You are now ready to inject.

Injecting

1. Hold the syringe in the hand you write with (like a pencil). With your other hand, gently pinch the cleaned area of your stomach between your forefinger and thumb to make a fold in the skin.

- Make sure you hold the skin fold throughout the injection.

2. Hold the syringe so that the needle is pointing straight down (at a 90° angle to your skin). Insert the full length of the needle into the skin fold.



3. Press down on the plunger with your thumb. This will inject the medicine into the fatty tissue of your stomach. Complete the injection by using all of the medicine in the syringe.

4. Remove the needle from the injection site by pulling it straight out. A protective sleeve will automatically cover the needle. You can now let go of the skin fold. The safety system only releases the protective sleeve when the syringe has been emptied by pressing the plunger all the way down.

When you have finished

1. To avoid bruising, do not rub the injection site after you have self-injected.

2. Throw the used syringe away in the container for sharp objects. Close the container lid tightly and place it out of the reach of children. When the container is full, dispose of it as your doctor or pharmacist has instructed.

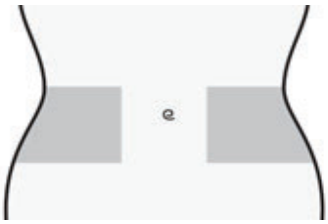
Any unused medicine or waste material should be disposed of in accordance with local requirements.

(Instructions for syringes with the PREVENTIS™ automatic safety system)

Preparing the injection site

1. Choose an area on the right or left side of your stomach, at least 5 centimeters away from your belly button and out towards your sides.

- Do not inject within 5 cm of your belly button or near scars or bruises.
- Alternate the injection site between the right and left sides of your stomach, depending on the area you last injected.



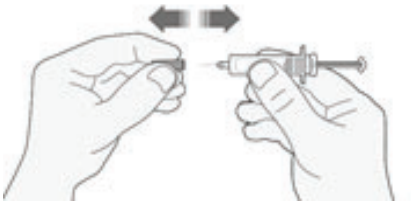
2. Wash your hands. Clean (do not rub) the area that you will inject with an alcohol swab or soap and water.

3. Sit or lie in a comfortable position so you are relaxed. Make sure you can see the place you are going to inject. A lounge chair, recliner, or bed propped up with pillows is ideal.

Selecting your dose

1. Carefully pull off the needle cap from the syringe. Throw away the cap.

- Do not press on the plunger to get rid of air bubbles before self-injecting, as you might lose some of the medicine.
- Once you have removed the cap, do not allow the needle to touch anything. This is to make sure the needle stays clean (sterile).



2. When the amount of medicine in the syringe already matches your prescribed dose, there is no need to adjust the dose. You are now ready to inject.

3. When the dose depends on your body weight, you may need to adjust the dose in the syringe to match the prescribed dose. In that case, you can get rid of any excess medicine by holding the syringe pointing down (to keep the air bubble in the syringe) and ejecting the extra amount into a container.

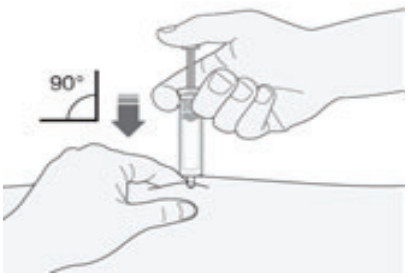
4. A drop may appear at the tip of the needle. If this occurs, remove the drop before injecting by tapping on the syringe with the needle pointing down. You are now ready to inject.

Injecting

1. Hold the syringe in the hand you write with (like a pencil). With your other hand, gently pinch the cleaned area of your stomach between your forefinger and thumb to make a fold in the skin.

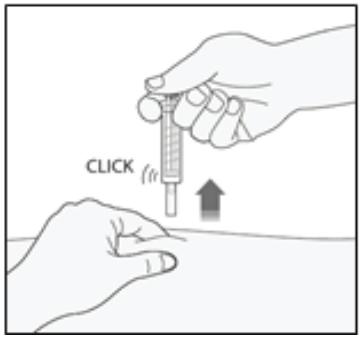
- Make sure you hold the skin fold throughout the injection.

2. Hold the syringe so that the needle is pointing straight down (at a 90° angle to your skin). Insert the full length of the needle into the skin fold.



3. Press down on the plunger with your thumb. This will inject the medicine into the fatty tissue of your stomach. Complete the injection by using all of the medicine in the syringe.

4. Remove the needle from the injection site by pulling it straight out, keeping your fingers on the plunger. Do not point the needle towards yourself or others, and activate the safety system by firmly pressing down the plunger. A protective sleeve will automatically cover the needle and you will hear a "click" to confirm shield activation. You can now let go of the skin fold.



When you have finished

1. To avoid bruising, do not rub the injection site after you have self-injected.

2. Throw the used syringe away in the container for sharp objects. Close the container lid tightly and place it out of the reach of children. When the container is full, dispose of it as your doctor or pharmacist has instructed.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Changing anticoagulant medicines

- **Changing from Lovenox to blood thinners called vitamin-K antagonists (such as warfarin)**
  Your doctor will ask you to have a blood test called INR and tell you when to stop **Lovenox**.
- **Changing from blood thinners called vitamin-K antagonists (such as warfarin) to Lovenox**
  Stop taking the vitamin-K antagonist. Your doctor will ask you to have a blood test called INR and tell you when to start **Lovenox**.
- **Changing from Lovenox to treatment with direct oral anticoagulant**
  Stop taking **Lovenox**. Start taking the direct oral anticoagulant 0-2 hours before the time you would have had the next injection, then continue as normal.
- **Changing from treatment with direct oral anticoagulant to Lovenox**
  Stop taking direct oral anticoagulant. Do not start treatment with **Lovenox** until 12 hours after the final dose of direct oral anticoagulant.

If you use more Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes than you should

If you think that you have used too much or too little **Lovenox**, tell your doctor, pharmacist or nurse immediately, even if you have no signs of a problem. If a child accidentally injects or swallows **Lovenox**, take them to a hospital casualty department straight away.

If you forget to use Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

If you forget to give yourself a dose, have it as soon as you remember. Do not give yourself a double dose on the same day to make up for a forgotten dose. Keeping a diary will help to make sure you do not miss a dose.

If you stop using Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

It is important for you to keep having **Lovenox** injections until your doctor decides to stop them. If you stop, you could get a blood clot which can be very dangerous.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop using Lovenox and talk to a doctor or nurse straight away if you get any signs of a severe allergic reaction (such as a rash, difficulty breathing or swallowing or swelling of the face, lips, mouth, throat or eyes).

Like other similar medicines (that reduce blood clotting), **Lovenox** may cause bleeding. This may potentially be life-threatening. In some cases the bleeding may not be obvious.

Talk to your doctor straight away if:

- you experience a bleeding event that does not stop by itself
- you experience signs of excessive bleeding, such as being very weak, tired, pale or dizzy with headache or unexplained swelling.

Your doctor may decide to keep you under closer observation or change your medicine.

Talk to your doctor straight away:

- if you have any sign of blockage of a blood vessel by a blood clot such as:
  - cramping pain, redness, warmth, or swelling in one of your legs – these are symptoms of deep vein thrombosis.
  - breathlessness, chest pain, fainting or coughing up blood – these are symptoms of a pulmonary embolism.
- if you have a painful rash of dark red spots under the skin which do not go away when you put pressure on them.

Your doctor may request you perform a blood test to check your platelet count.

Other side effects

Very common (may affect more than 1 in 10 people):

- Bleeding.
- Increases in liver enzymes.

Common (may affect up to 1 in 10 people):

- You bruise more easily than usual. This could be because of a blood problem with low platelet counts.
- Pink patches on your skin. These are more likely to appear in the area you have been injected with **Lovenox**.
- Skin rash (hives).
- Itchy red skin.
- Bruising or pain at the injection site.
- Decreased red blood cell count.
- High platelet counts in the blood.
- Headache.

Uncommon (may affect up to 1 in 100 people):

- Sudden severe headache. This could be a sign of bleeding in the brain.
- A feeling of tenderness and swelling in your stomach. You may have bleeding in your stomach.

- Large red irregularly shaped skin lesions with or without blisters.
- Skin irritation (local irritation).
- Yellowing of your skin or eyes and your urine becomes darker in color. This could be a liver problem.

Rare (may affect up to 1 in 1 000 people):

- Severe allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- Increased potassium in your blood. This is more likely to happen in people with kidney problems or diabetes. Your doctor will be able to check this by carrying out a blood test.
- An increase in the number of eosinophils in your blood. Your doctor will be able to check this by carrying out a blood test.
- Hair loss.
- Osteoporosis (a condition where your bones are more likely to break) after long term use
- Tingling, numbness and muscular weakness (particularly in the lower part of your body) when you have had a spinal puncture or a spinal anesthetic.
- Loss of control over your bladder or bowel (so you cannot control when you go to the toilet).
- Hard mass or lump at the injection site.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the French national reporting system: i.e. *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (ANSM) under *"Réseau des Centres de Pharmacovigilance"* (Network of Pharmacovigilance Centers) - Website: www.ansm.sante.fr

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE LOVENOX 6 000 IU (60 MG)/0.6 ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGES

Do not store above 25 °C. Do not freeze.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the syringe is damaged, there are bits in the solution or the solution is an abnormal color (see "What **Lovenox** 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes looks like and contents of the pack").

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes contains

- The active substance is: enoxaparin sodium.
  Each milliliter contains 100 mg of enoxaparin sodium, equivalent to 10 000 IU anti-Xa activity.
  One 0.6 mL pre-filled syringe contains 6 000 IU anti-Xa, equivalent to 60 mg of enoxaparin sodium.
- The other ingredient is:
  Water for injection.

What Lovenox 6 000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes looks like and contents of the pack

Lovenox is a clear, colorless to yellowish solution for injection in glass pre-filled syringes (with or without an automatic safety system).

Boxes of 2, 5, 6, 10, 12, 20, 24, 30, 50 or 100 pre-filled syringes, and multi-packs of 3 x 10 and 9 x 10 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorization Holder

Sanofi-Aventis France
82, avenue Raspail
94250 Gentilly
France

Operator

Sanofi-Aventis France
82, avenue Raspail
94250 Gentilly
France

Manufacturer

Sanofi Winthrop Industrie
Boulevard industriel,
Zone industrielle
76580 Le Trait
France

or

Sanofi Winthrop Industrie
180, rue Jean Jaurès
94700 Maisons-Alfort
France

or

Chinoin Pharmaceutical and Chemical Works Private Co. Ltd
Csanyikvolgy Site
Miskolc, Csanyikvolgy H 3510
Hungary

or

Sanofi-Aventis Private Co. Ltd
Budapest Logistics and Distribution Platform
Bdg. DC5, Campona Utcal
Budapest, 1225
Hungary

or

Sanofi-Aventis GmbH
Saturn Tower, Leonard Bernstein Strasse 10
1220 Vienna
Austria

Names of the medicinal product in the Member States of the European Economic Area

This medicinal product is authorized in the Member States of the EEA under the following names: As per local requirements.
[To be completed subsequently by the Marketing Authorization holder]

This leaflet was last revised in:

[To be completed subsequently by the Marketing Authorization holder]

Other

Detailed information on this medicine is available on the ANSM website (France).