ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

10,000 IU/mL (100 mg/mL) solution for injection:
- LOVENOX (and associated names) 2,000 IU (20 mg)/0.2 mL solution for injection
- LOVENOX (and associated names) 4,000 IU (40 mg)/0.4 mL solution for injection
- LOVENOX (and associated names) 6,000 IU (60 mg)/0.6 mL solution for injection
- LOVENOX (and associated names) 8,000 IU (80 mg)/0.8 mL solution for injection
- LOVENOX (and associated names) 10,000 IU (100 mg)/1 mL solution for injection

- LOVENOX (and associated names) 30,000 IU (300 mg)/3 mL solution for injection
- LOVENOX (and associated names) 50,000 IU (500 mg)/5 mL solution for injection
- LOVENOX (and associated names) 100,000 IU (1,000 mg)/10 mL solution for injection

15,000 IU/mL (150 mg/mL) solution for injection:
- LOVENOX (and associated names) 12,000 IU (120 mg)/0.8 mL solution for injection
- LOVENOX (and associated names) 15,000 IU (150 mg)/1 mL solution for injection

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10,000 IU/mL (100 mg/mL) solution for injection

Pre-Filled Syringes:
2,000 IU (20 mg) /0.2 mL
Each prefilled syringe contains enoxaparin sodium 2,000 IU anti-Xa activity (equivalent to 20 mg) in 0.2 mL water for injections.
4,000 IU (40 mg) /0.4 mL
Each prefilled syringe contains enoxaparin sodium 4,000 IU anti-Xa activity (equivalent to 40 mg) in 0.4 mL water for injections.
6,000 IU (60 mg) /0.6 mL
Each prefilled syringe contains enoxaparin sodium 6,000 IU anti-Xa activity (equivalent to 60 mg) in 0.6 mL water for injections.
8,000 IU (80 mg) /0.8 mL
Each prefilled syringe contains enoxaparin sodium 8,000 IU anti-Xa activity (equivalent to 80 mg) in 0.8 mL water for injections.
10,000 IU (100 mg) /1.0 mL
Each prefilled syringe contains enoxaparin sodium 10,000 IU anti-Xa activity (equivalent to 100 mg) in 1.0 mL water for injections.

For the full list of excipients, see section 6.1.

Ampoules
10,000 IU (100 mg) /1.0 mL
Each ampoule contains enoxaparin sodium 10,000 IU anti-Xa activity (equivalent to 100 mg) in 1.0 mL water for injections.

For the full list of excipients, see section 6.1.

Multiple Dose Vials:
30,000 IU (300 mg) /3 mL
One vial contains enoxaparin sodium 30,000 IU anti-Xa activity (equivalent to 300 mg) + 45 mg benzyl alcohol in 3.0 mL water for injections.

50,000 IU (500 mg)/5 mL
One vial contains enoxaparin sodium 50,000 IU anti-Xa activity (equivalent to 500 mg) + 75 mg benzyl alcohol in 5.0 mL water for injections.
100,000 IU (1000 mg)/10 mL
One vial contains enoxaparin sodium 100,000 IU anti-Xa activity (equivalent to 1000 mg) + 150 mg benzyl alcohol in 10.0 mL water for injections.

Excipient(s) with known effect: benzyl alcohol.
For the full list of excipients, see section 6.1.

15,000 IU/mL (150 mg/mL) solution for injection
Pre-Filled Syringes:
12,000 IU (120 mg) / 0.8 mL
Each prefilled syringe contains enoxaparin sodium 12,000 IU anti-Xa activity (equivalent to 120 mg) in 0.8 mL water for injections.
15,000 IU (150 mg) /1 mL
Each prefilled syringe contains enoxaparin sodium 15,000 IU anti-Xa activity (equivalent to 150 mg) in 1.0 mL water for injections.

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.

[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOVENOX (and associated names) is indicated in adults for:
- Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery.
- 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 haemodialysis.
- Acute coronary syndrome:
    - Treatment of unstable angina and Non ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid.
    - Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

4.2 Posology and method of administration

Posology

Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients
Individual thromboembolic risk for patients can be estimated using validated risk stratification model.

- In patients at moderate risk of thromboembolism, the recommended dose of enoxaparin sodium is 2,000 IU (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 orthopaedic surgery), the last injection should be administered no later than 12 hours prior to surgery and resumed 12 hours after surgery.
    - For patients who undergo major orthopaedic surgery an extended thromboprophylaxis up to 5 weeks is recommended.
    - For patients with a high venous thromboembolism (VTE) risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks is recommended.

Prophylaxis of venous thromboembolism in medical patients
The recommended dose of enoxaparin sodium is 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 haemodialysis
The recommended dose is 100 IU/kg (1 mg/kg) of enoxaparin sodium.
For patients with a high risk of haemorrhage, 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 haemodialysis, enoxaparin sodium should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 50 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 haemodialysis 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.

Paediatric population

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

Multiple dose vials containing benzyl alcohol

LOVENOX (and associated names) contains benzyl alcohol and must not be used in newborn and premature neonates (see section 4.3).

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 haemodialysis.

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

Indication	Dosing regimen
Prophylaxis of venous thromboembolic disease	2,000 IU (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 haemodialysis indication.

- Moderate and mild renal impairment

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

Method of administration

LOVENOX (and associated names) 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 haemodialysis, it is administered through the arterial line of a dialysis circuit.

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

The use of a tuberculin syringe or equivalent is recommended when using ampoules or multiple-dose vials to assure withdrawal of the appropriate volume of drug.

- 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 (see instructions in section 6.6).

In case of self-administration, patient should be advised to follow instructions provided in the patient information leaflet included in the pack of this medicine.

- IV (bolus) injection (for acute STEMI indication only):

For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection.
For IV injection, either the multidose vial or prefilled 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 haemodialysis.

Switch between enoxaparin sodium and oral anticoagulants

- *Switch between enoxaparin sodium and vitamin K antagonists (VKA)*

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

- *Switch between enoxaparin sodium and direct oral anticoagulants (DOAC)*

For patients currently receiving enoxaparin sodium, discontinue enoxaparin sodium and start the DOAC 0 to 2 hours before the time that the next scheduled administration of enoxaparin sodium would be due as per DOAC label.

For patients currently receiving a DOAC, the first dose of enoxaparin sodium should be given at the time the next DOAC dose would be taken.

Administration in spinal/epidural anaesthesia or lumbar puncture

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

- *At doses used for treatment*

  A puncture-free interval of at least 24 hours shall be kept between the last injection of enoxaparin sodium at curative doses and the needle or catheter placement (see also section 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 haemorrhage, including recent haemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities;
- Spinal or epidural anaesthesia or loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24 hours (see section 4.4).

Multiple dose vials containing benzyl alcohol

- Hypersensitivity to benzyl alcohol;
- Because of the content of benzyl alcohol (see section 6.1), enoxaparin sodium multiple dose vial formulation must not be given to newborns or premature neonates (see sections 4.4 and 4.6).

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.

- *Haemorrhage*

As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted.
Enoxaparin sodium, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as:

- impaired haemostasis,
- history of peptic ulcer,
- recent ischemic stroke,
- severe arterial hypertension,
- recent diabetic retinopathy,
- neuro- or ophthalmologic surgery,
- concomitant use of medications affecting haemostasis (see section 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 anaesthesia or lumbar puncture*

Spinal/epidural anaesthesia or lumbar puncture must not be performed within 24 hours of administration of enoxaparin sodium at therapeutic doses (see also section 4.3).
There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture procedures resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 4,000 IU (40 mg) once daily or lower. The risk of these events is higher with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting haemostasis such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anaesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium (see section 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 anaesthesia/analgesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

- *Skin necrosis / cutaneous vasculitis*

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

- *Percutaneous coronary revascularization procedures*

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, NSTEMI and acute STEMI, adhere precisely to the intervals recommended between enoxaparin sodium injection doses. It is important to achieve haemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation.

- *Acute infective endocarditis*

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

- *Mechanical prosthetic heart valves*

The use of enoxaparin sodium has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin sodium for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and foetal death.

- *Pregnant women with mechanical prosthetic heart valves*

The use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin sodium (100 IU/kg (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 foetal 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 haemodialysis.
In patients with severe renal impairment (creatinine clearance 15-30 mL/min), since exposure of enoxaparin sodium is significantly increased, a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges (see section 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/m2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

- *Hyperkalaemia*

Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia (see section 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.

Multiple dose vials containing benzyl alcohol

- *Benzyl alcohol*

The administration of medicinal product containing benzyl alcohol as a preservative to neonates has been associated with a fatal "Gasping Syndrome" (see section 4.3). Benzyl alcohol may also cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended:

- *Medicinal products affecting haemostasis (see section 4.4)*

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

- Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac,
- Other thrombolytics (e.g. alteplase, reteplase, streptokinase, tenecteplase, urokinase) and anticoagulants (see section 4.2).

Concomitant use with caution:

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

- *Other medicinal products affecting haemostasis such as:*
  - Platelet aggregation inhibitors including acetylsalicylic acid used at antiaggregant dose (cardioprotection), clopidogrel, ticlopidine, and glycoprotein IIb/IIIa antagonists indicated in acute coronary syndrome due to the risk of bleeding,
  - Dextran 40,
  - Systemic glucocorticoids.

- *Medicinal products increasing potassium levels:*

Medicinal products that increase serum potassium levels may be administered concurrently with enoxaparin sodium under careful clinical and laboratory monitoring (see sections 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 foetotoxicity 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 haemorrhagic risk. Overall, the data suggest that there is no evidence for an increased risk of haemorrhage, thrombocytopenia or osteoporosis with respect to the risk observed in non-pregnant women, other than that observed in pregnant women with prosthetic heart valves (see section 4.4).

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

Multiple dose vials containing benzyl alcohol

As benzyl alcohol may cross the placenta, it is recommended to use a formulation that does not contain benzyl alcohol.

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 (and associated names) 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 orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1,169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of DVT with or without PE, 1,578 for treatment of unstable angina and non-Q-wave myocardial infarction and 10,176 for treatment of acute STEMI.

Enoxaparin sodium regimen administered during these clinical trials varies depending on indications. The enoxaparin sodium dose was 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, haemorrhages, 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); and very rare (< 1/10,000) or not known (cannot be estimated from available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
- Common: Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis
- Rare: Eosinophilia*
- Rare: Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (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 haematoma* (or neuraxial haematoma). These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section 4.4).

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

Musculoskeletal, connective tissue and bone disorders
- Rare: Osteoporosis* following long term therapy (greater than 3 months)

General disorders and administration site conditions

- Common: Injection site haematoma, injection site pain, other injection site reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction)
- Uncommon: Local irritation, skin necrosis at injection site

Investigations

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

Description of selected adverse reactions

Haemorrhages

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

As with other anticoagulants, haemorrhage may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see sections 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*: **Haemorrhage** [α] *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α]	*Very common:* **Haemorrhage** [α] *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α] *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α] *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**

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

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

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

Multiple dose vials containing benzyl alcohol:
The administration of medicinal product containing benzyl alcohol as a preservative to neonates has been associated with a fatal "Gasping Syndrome" (see section 4.3).
Benzyl alcohol may also cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 national reporting system listed in Appendix V.

4.9 Overdose

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

Management
The anticoagulant effects can be largely neutralized by the slow IV injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected; 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: B01A B05

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 orthopaedic surgery

In a double blind study of extended prophylaxis for patients undergoing hip replacement surgery, 179 patients with no venous thromboembolic disease initially treated, while hospitalized, with enoxaparin sodium 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 SC enoxaparin sodium 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT. Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilization, revascularization procedures or hospital discharge. The patients had to be followed up to 30 days. In comparison with heparin, enoxaparin sodium significantly reduced the combined incidence of angina pectoris, myocardial infarction and death, with a decrease of 19.8 to 16.6% (relative risk reduction of 16.2%) on day 14. This reduction in the combined incidence was maintained after 30 days (from 23.3 to 19.8%; relative risk reduction of 15%).
There were no significant differences in major haemorrhages, although a haemorrhage at the site of the SC injection was more frequent.

Treatment of acute ST-segment elevation myocardial infarction
In a large multicenter study, 20,479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium in a single 3,000 IU (30 mg) IV bolus plus a 100 IU/kg (1 mg/kg) SC dose followed by an SC injection of 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT for 48 hours. All patients were also treated with acetylsalicylic acid for a minimum of 30 days. The enoxaparin sodium dosing strategy was adjusted for severe renally impaired patients and for the elderly of at least 75 years of age. The SC injections of enoxaparin sodium were given until hospital discharge or for a maximum of eight days (whichever came first).
4,716 patients underwent percutaneous coronary intervention receiving antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin sodium, the PCI was to be performed on enoxaparin sodium (no switch) using the regimen established in previous studies i.e. no additional dosing, if last SC administration given less than 8 hours before balloon inflation, IV bolus of 30 IU/ kg (0.3 mg/kg) enoxaparin sodium, if the last SC administration given more than 8 hours before balloon inflation.
Enoxaparin sodium compared to unfractionated heparin significantly decreased the incidence of the primary end point, a composite of death from any cause or myocardial re-infarction in the first 30 days

after randomization [9.9 percent in the enoxaparin sodium group, as compared with 12.0 percent in the unfractionated heparin group] with a 17 percent relative risk reduction ($p<0.001$).
The treatment benefits of enoxaparin sodium, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35 percent reduction in the relative risk of myocardial re-infarction, as compared with treatment with unfractionated heparin ($p<0.001$).
The beneficial effect of enoxaparin sodium on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, type of fibrinolytic administered, and time to treatment with study drug.
There was a significant treatment benefit of enoxaparin sodium, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomization (23 percent reduction in relative risk) or who were treated medically (15 percent reduction in relative risk, $p=0.27$ for interaction).
The rate of the 30 day composite endpoint of death, myocardial re-infarction or intracranial haemorrhage (a measure of net clinical benefit) was significantly lower ($p<0.0001$) in the enoxaparin sodium group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favour of treatment with enoxaparin sodium.
The incidence of major bleeding at 30 days was significantly higher ($p<0.0001$) in the enoxaparin sodium group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin sodium group (0.5%) versus the heparin group (0.1%), while the incidence of intracranial haemorrhage was similar in both groups (0.8% with enoxaparin sodium versus 0.7% with heparin).
The beneficial effect of enoxaparin sodium on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period.

Hepatic impairment
Based on literature data the use of enoxaparin sodium 4,000 IU (40 mg) in cirrhotic patients (Child-Pugh class B-C) appears to be safe and effective in preventing portal vein thrombosis. It should be noted that the literature studies may have limitations. Caution should be used in patients with hepatic impairment as these patients have an increased potential for bleeding (see section 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 litres and is close to the blood volume.

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

Elimination
Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 L/h after a 150 IU /kg (1.5 mg/kg) 6-hour IV infusion.
Elimination appears monophasic with a half-life of about 5 hours after a single SC dose to about 7 hours after repeated dosing.
Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

Special populations
Elderly
Based on the results of a population pharmacokinetic analysis, the enoxaparin sodium kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see sections 4.2 and 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).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

SC injection
Do not mix with other products.

IV (Bolus) Injection (for acute STEMI indication only):
Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water (see section 4.2).

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

INSTRUCTIONS FOR USE: PREFILLED SYRINGE
[To be completed nationally]

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
{DD/MM/YYYY}
{DD month YYYY}

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS Agency (link)}

1. NAME OF THE MEDICINAL PRODUCT

LOVENOX (and associated names) 10,000 IU (100 mg)/10 mL solution for injection
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains enoxaparin sodium 10,000 IU anti-Xa activity (equivalent to 100 mg) in 10 mL water for injections.
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.

[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOVENOX (and associated names) is indicated in adults for:
- Prevention of thrombus formation in extra corporeal circulation during haemodialysis.

4.2 Posology and method of administration

Posology

Prevention of thrombus formation during haemodialysis
The recommended dose is 100 IU/kg (1 mg/kg) of enoxaparin sodium.
For patients with a high risk of haemorrhage, 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 haemodialysis, enoxaparin sodium should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 50 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 haemodialysis sessions.

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

Elderly
No dose reduction is necessary in the elderly patients in haemodialysis indication.

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).

Method of administration
LOVENOX (and associated names) should not be administered by the intramuscular route.

- Arterial line injection:

It is administered through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extra corporeal circulation during haemodialysis.

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 haemorrhage, including recent haemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities;
- Spinal or epidural anaesthesia or loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24 hours (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.

- *Haemorrhage*

As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted.
Enoxaparin sodium, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as:

- impaired haemostasis,
- history of peptic ulcer,
- recent ischemic stroke,
- severe arterial hypertension,
- recent diabetic retinopathy,
- neuro- or ophthalmologic surgery,
- concomitant use of medications affecting haemostasis (see section 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 anaesthesia or lumbar puncture*

Spinal/epidural anaesthesia or lumbar puncture must not be performed within 24 hours of administration of enoxaparin at therapeutic doses (see also section 4.3).
There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture procedures resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 4,000 IU (40 mg) once daily or lower. The risk of these events is higher with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting haemostasis such as Non-Steroidal-Anti Inflammatory Drugs (NSAIDs), with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anaesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium (see section 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.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anaesthesia/analgesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits

(numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

- *Skin necrosis / cutaneous vasculitis*

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

- *Acute infective endocarditis*

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

- *Mechanical prosthetic heart valves*

The use of enoxaparin sodium has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin sodium for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and foetal death.

- *Pregnant women with mechanical prosthetic heart valves*

The use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin sodium (100 IU/kg (1 mg/kg) twice daily) to reduce the risk of thrombo-embolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal 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 ST-segment elevation myocardial infarction (STEMI) (see section 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 section 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 haemodialysis.
In patients with severe renal impairment (creatinine clearance 15-30 mL/min), since exposure of enoxaparin sodium is significantly increased, a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges.
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/m2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

- *Hyperkalaemia*

Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia (see section 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 haemostasis (see section 4.4)*

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

- Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac,
- Other thrombolytics (e.g. alteplase, reteplase, streptokinase, tenecteplase, urokinase) and anticoagulants.

Concomitant use with caution:

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

- *Other medicinal products affecting haemostasis such as:*
  - Platelet aggregation inhibitors including acetylsalicylic acid used at antiaggregant dose (cardioprotection), clopidogrel, ticlopidine, and glycoprotein IIb/IIIa antagonists indicated in acute coronary syndrome due to the risk of bleeding,
  - Dextran 40,
  - Systemic glucocorticoids.

- *Medicinal products increasing potassium levels:*

Medicinal products that increase serum potassium levels may be administered concurrently with enoxaparin sodium under careful clinical and laboratory monitoring (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 foetotoxicity 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 haemorrhagic risk. Overall, the data suggest that there is no evidence for an increased risk of haemorrhage, thrombocytopenia or osteoporosis with respect to the risk observed in non-pregnant women, other than that observed in pregnant women with prosthetic heart valves (see section 4.4).

If an epidural anaesthesia 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 (and associated names) 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 (DVT) following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1,169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of DVT with or without pulmonary embolism (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) subcutaneous (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, haemorrhages, 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); and very rare (< 1/10,000) or not known (cannot be estimated from available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
- Common: Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis
- Rare: Eosinophilia*
- Rare: Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (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 haematoma* (or neuraxial haematoma). These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section 4.4).

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

Musculoskeletal, connective tissue and bone disorders
- Rare: Osteoporosis* following long term therapy (greater than 3 months)

General disorders and administration site conditions

- Common: Injection site haematoma, injection site pain, other injection site reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction)
- Uncommon: Local irritation, skin necrosis at injection site

Investigations

- Rare: Hyperkalaemia* (see sections 4.4 and 4.5)

Description of selected adverse reactions

Haemorrhages

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

As with other anticoagulants, haemorrhage may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see sections 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*: **Haemorrhage** [α] *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α]	*Very common:* **Haemorrhage** [α] *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α] *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α] *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**

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

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

Paediatric 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 authorisation 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 national reporting system listed in Appendix V.

4.9 Overdose

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

Management
The anticoagulant effects can be largely neutralized by the slow IV injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected; 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: B01A B05

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

In a double blind study of extended prophylaxis for patients undergoing hip replacement surgery, 179 patients with no venous thromboembolic disease initially treated, while hospitalized, with enoxaparin sodium 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 1073 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 International Normalized Ratio (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 (1mg/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 SC enoxaparin sodium 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT. Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilization, revascularization procedures or hospital discharge. The patients had to be followed up to 30 days. In comparison with heparin, enoxaparin sodium significantly reduced the combined incidence of angina pectoris, myocardial infarction and death, with a decrease of 19.8 to 16.6% (relative risk reduction of 16.2%) on day 14. This reduction in the combined incidence was maintained after 30 days (from 23.3 to 19.8%; relative risk reduction of 15%).
There were no significant differences in major haemorrhages, although a haemorrhage at the site of the SC injection was more frequent.

Treatment of acute ST-segment elevation myocardial infarction
In a large multicenter study, 20,479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium in a single 3,000 IU (30 mg) IV bolus plus a 100 IU/kg (1 mg/kg) SC dose followed by an SC injection of 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT for 48 hours. All patients were also treated with acetylsalicylic acid for a minimum of 30 days. The enoxaparin sodium dosing strategy was adjusted for severe renally impaired patients and for the elderly of at least 75 years of age. The SC injections of enoxaparin sodium were given until hospital discharge or for a maximum of eight days (whichever came first).
4,716 patients underwent percutaneous coronary intervention (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 haemorrhage (a measure of net clinical benefit) was significantly lower (p<0.0001) in the enoxaparin sodium group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favour of treatment with enoxaparin sodium.
The incidence of major bleeding at 30 days was significantly higher (p<0.0001) in the enoxaparin sodium group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin sodium group (0.5%) versus the heparin group (0.1%), while the incidence of intracranial haemorrhage was similar in both groups (0.8% with enoxaparin sodium versus 0.7% with heparin).
The beneficial effect of enoxaparin sodium on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period.

Hepatic impairment
Based on literature data the use of enoxaparin sodium 4,000 IU (40 mg) in cirrhotic patients (Child-Pugh class B-C) appears to be safe and effective in preventing portal vein thrombosis. It should be noted that the literature studies may have limitations. Caution should be used in patients with hepatic impairment as these patients have an increased potential for bleeding (see section 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 litres and is close to the blood volume.

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

Elimination
Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 L/h after a 150 IU /kg (1.5 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 section 4.4).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.6 Nature and contents of container

[To be completed nationally]

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

[To be completed nationally]

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
{DD/MM/YYYY}
{DD month YYYY}

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS Agency (link)}

1. NAME OF THE MEDICINAL PRODUCT

LOVENOX (and associated names) 10 x 4,000 IU (10 x 40 mg) solution for injection
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 3.0 mL pen contains enoxaparin sodium 40,000 IU anti-Xa activity (equivalent to 400 mg), equivalent to 10 single doses of 4,000 IU (40 mg) enoxaparin sodium, + 45 mg benzyl alcohol in 3.0 mL water for injections

Excipient(s) with known effect: benzyl alcohol.
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.

[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOVENOX (and associated names) is indicated in adults for:

- Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery.
- 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.
- 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 orthopaedic surgery), the last injection should be administered no later than 12 hours prior to surgery and resumed 12 hours after surgery.
    - For patients who undergo major orthopaedic surgery an extended thromboprophylaxis up to 5 weeks is recommended.
    - For patients with a high venous thromboembolism (VTE) risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks is recommended.

Prophylaxis of venous thromboembolism in medical patients
The recommended dose of enoxaparin sodium is 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).

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.

Paediatric population
The safety and efficacy of enoxaparin sodium in paediatric population have not been established. LOVENOX (and associated names) contains benzyl alcohol and must not be used in newborn and premature neonates (see section 4.3).

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 haemodialysis.

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

Indication	Dosing regimen
Prophylaxis of venous thromboembolic disease	2,000 IU (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

- 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 (and associated names) 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 is administered by SC injection.
- For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection.
- SC injection technique:

Injection should be made preferably when the patient is lying down. Enoxaparin sodium is administered by deep SC injection.

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.

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.

Switch between enoxaparin sodium and oral anticoagulants

- *Switch between enoxaparin sodium and vitamin K antagonists (VKA)*

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

- *Switch between enoxaparin sodium and direct oral anticoagulants (DOAC)*

For patients currently receiving enoxaparin sodium, discontinue enoxaparin sodium and start the DOAC 0 to 2 hours before the time that the next scheduled administration of enoxaparin sodium would be due as per DOAC label.
For patients currently receiving a DOAC, the first dose of enoxaparin sodium should be given at the time the next DOAC dose would be taken.

Administration in spinal/epidural anaesthesia or lumbar puncture

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

- *At doses used for treatment*

A puncture-free interval of at least 24 hours shall be kept between the last injection of enoxaparin sodium at curative doses and the needle or catheter placement (see also section 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), to benzyl alcohol 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 haemorrhage, including recent haemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities;
- Spinal or epidural anaesthesia or loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24 hours (see section 4.4).
- Because of the content of benzyl alcohol (see section 6.1), enoxaparin sodium pen formulation must not be given to newborns or premature neonates (see sections 4.4 and 4.6).

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.

- *Haemorrhage*

As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted.
Enoxaparin sodium, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as:

- impaired haemostasis,
- history of peptic ulcer,
- recent ischemic stroke,
- severe arterial hypertension,
- recent diabetic retinopathy,
- neuro- or ophthalmologic surgery,
- concomitant use of medications affecting haemostasis (see section 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 anaesthesia or lumbar puncture*

Spinal/epidural anaesthesia or lumbar puncture must not be performed within 24 hours of administration of enoxaparin at therapeutic doses (see also section 4.3).
There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture procedures resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 4,000 IU (40 mg) once daily or lower. The risk of these events is higher with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting haemostasis such as Non-Steroidal Anti Inflammatory Drugs (NSAIDs), with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anaesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium (see section 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 anaesthesia/analgesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

- *Skin necrosis / cutaneous vasculitis*

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

- *Percutaneous coronary revascularization procedures*

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, NSTEMI and acute STEMI, adhere precisely to the intervals recommended between enoxaparin sodium injection doses. It is important to achieve haemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation

- *Acute infective endocarditis*

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

- *Mechanical prosthetic heart valves*

The use of enoxaparin sodium has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin sodium for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and foetal death.

- *Pregnant women with mechanical prosthetic heart valves*

The use of enoxaparin sodium for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin sodium (100 IU/kg (1 mg/kg) twice daily) to reduce the risk of thrombo-embolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal 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 haemodialysis.
In patients with severe renal impairment (creatinine clearance 15-30 mL/min), since exposure of enoxaparin sodium is significantly increased, a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges (see section 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/m2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

- *Hyperkalaemia*

Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia (see section 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.

- *Benzyl alcohol*

The administration of medicinal product containing benzyl alcohol as a preservative to neonates has been associated with a fatal “Gasping Syndrome” (see section 4.3). Benzyl alcohol may also cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Concomitant use not recommended:</u>

- *Medicinal products affecting haemostasis (see section 4.4)*

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

- Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac,
- Other thrombolytics (e.g. alteplase, reteplase, streptokinase, tenecteplase, urokinase) and anticoagulants (see section 4.2).

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

- *Other medicinal products affecting haemostasis such as:*
  - Platelet aggregation inhibitors including acetylsalicylic acid used at antiaggregant dose (cardioprotection), clopidogrel, ticlopidine, and glycoprotein IIb/IIIa antagonists indicated in acute coronary syndrome due to the risk of bleeding,
  - Dextran 40,
  - Systemic glucocorticoids.

- *Medicinal products increasing potassium levels:*

Medicinal products that increase serum potassium levels may be administered concurrently with enoxaparin sodium under careful clinical and laboratory monitoring (see sections 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 foetotoxicity 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 haemorrhagic risk. Overall, the data suggest that there is no evidence for an increased risk of haemorrhage, thrombocytopenia or osteoporosis with respect to the risk observed in non-pregnant women, other than that observed in pregnant women with prosthetic heart valves (see section 4.4).

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

As benzyl alcohol may cross the placenta, it is recommended to use a formulation that does not contain benzyl alcohol.

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 (and associated names) 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 1776 for prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1,169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of DVT with or without PE, 1,578 for treatment of unstable angina and non-Q-wave myocardial infarction and 10,176 for treatment of acute STEMI.

Enoxaparin sodium regimen administered during these clinical trials varies depending on indications. The enoxaparin sodium dose was 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, haemorrhages, 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); and very rare (< 1/10,000) or not known (cannot be estimated from available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
- Common: Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis
- Rare: Eosinophilia*
- Rare: Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (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 haematoma* (or neuraxial haematoma). These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section 4.4).

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

Musculoskeletal, connective tissue and bone disorders
- Rare: Osteoporosis* following long term therapy (greater than 3 months)

General disorders and administration site conditions
- Common: Injection site haematoma, injection site pain, other injection site reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction)
- Uncommon: Local irritation, skin necrosis at injection site

Investigations
- Rare: Hyperkalaemia* (see sections 4.4 and 4.5)

Description of selected adverse reactions
Haemorrhages
These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients). Some of these cases have been fatal. In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by a haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.
As with other anticoagulants, haemorrhage may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see sections 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*: **Haemorrhage** [α] *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α]	*Very common:* **Haemorrhage** [α] *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α] *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage** [α] *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**

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

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

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

The administration of medicinal product containing benzyl alcohol as a preservative to neonates has been associated with a fatal "Gasping Syndrome" (see section 4.3).
Benzyl alcohol may also cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 national reporting system listed in Appendix V.

4.9 Overdose

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

Management
The anticoagulant effects can be largely neutralized by the slow IV injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected; 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: B01A B05

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

In a double blind study of extended prophylaxis for patients undergoing hip replacement surgery, 179 patients with no venous thromboembolic disease initially treated, while hospitalized, with enoxaparin sodium 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 1073 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 (1mg/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 SC enoxaparin sodium 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT. Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilization, revascularization procedures or hospital discharge. The patients had to be followed up to 30 days. In comparison with heparin, enoxaparin sodium significantly reduced the combined incidence of angina pectoris, myocardial infarction and death, with a decrease of 19.8 to 16.6% (relative risk reduction of 16.2%) on day 14. This reduction in the combined incidence was maintained after 30 days (from 23.3 to 19.8%; relative risk reduction of 15%).

There were no significant differences in major haemorrhages, although a haemorrhage at the site of the SC injection was more frequent.

Treatment of acute ST-segment elevation myocardial infarction
In a large multicenter study, 20,479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium in a single 3,000 IU (30 mg) IV bolus plus a 100 IU/kg (1 mg/kg) SC dose followed by an SC injection of 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT for 48 hours. All patients were also treated with acetylsalicylic acid for a minimum of 30 days. The enoxaparin sodium dosing strategy was adjusted for severe renally impaired patients and for the elderly of at least 75 years of age. The SC injections of enoxaparin sodium were given until hospital discharge or for a maximum of eight days (whichever came first).
4,716 patients underwent percutaneous coronary intervention receiving antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin sodium, the PCI was to be performed on enoxaparin sodium (no switch) using the regimen established in previous studies i.e. no additional dosing, if last SC administration given less than 8 hours before balloon inflation, IV bolus of 30 IU/ kg (0.3 mg/kg) enoxaparin sodium, if the last SC administration given more than 8 hours before balloon inflation.
Enoxaparin sodium compared to unfractionated heparin significantly decreased the incidence of the primary end point, a composite of death from any cause or myocardial re-infarction in the first 30 days after randomization [9.9 percent in the enoxaparin sodium group, as compared with 12.0 percent in the unfractionated heparin group] with a 17 percent relative risk reduction ($p<0.001$).
The treatment benefits of enoxaparin sodium, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35 percent reduction in the relative risk of myocardial re-infarction, as compared with treatment with unfractionated heparin ($p<0.001$).
The beneficial effect of enoxaparin sodium on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, type of fibrinolytic administered, and time to treatment with study drug.
There was a significant treatment benefit of enoxaparin sodium, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomization (23 percent reduction in relative risk) or who were treated medically (15 percent reduction in relative risk, $p=0.27$ for interaction).
The rate of the 30 day composite endpoint of death, myocardial re-infarction or intracranial haemorrhage (a measure of net clinical benefit) was significantly lower ($p<0.0001$) in the enoxaparin sodium group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favour of treatment with enoxaparin sodium.
The incidence of major bleeding at 30 days was significantly higher ($p<0.0001$) in the enoxaparin sodium group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin sodium group (0.5%) versus the heparin group (0.1%), while the incidence of intracranial haemorrhage was similar in both groups (0.8% with enoxaparin sodium versus 0.7% with heparin).
The beneficial effect of enoxaparin sodium on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period.

Hepatic impairment
Based on literature data the use of enoxaparin sodium 4,000 IU (40 mg) in cirrhotic patients (Child-Pugh class B-C) appears to be safe and effective in preventing portal vein thrombosis. It should be noted that the literature studies may have limitations. Caution should be used in patients with hepatic impairment as these patients have an increased potential for bleeding (see section 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 litres and is close to the blood volume.

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

Elimination

Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 L/h after a 150 IU /kg (1.5 mg/kg) 6-hour IV infusion.
Elimination appears monophasic with a half-life of about 5 hours after a single SC dose to about 7 hours after repeated dosing.
Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

Special populations

Elderly

Based on the results of a population pharmacokinetic analysis, the enoxaparin sodium kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see sections 4.2 and 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 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).

Haemodialysis

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

SC injection
Do not mix with other products.

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

INSTRUCTIONS FOR USE: [To be completed nationally]

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
{DD/MM/YYYY}
{DD month YYYY}

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS Agency (link)}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX PRE FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

LOVENOX (and associated names) 2,000 IU (20 mg)/0.2 mL solution for injection
LOVENOX (and associated names) 4,000 IU (40 mg /0.4 mL solution for injection
LOVENOX (and associated names) 6,000 IU (60 mg)/0.6 mL solution for injection
LOVENOX (and associated names) 8,000 IU (80 mg)/0.8 mL solution for injection
LOVENOX (and associated names) 10,000 IU (100 mg)/1 mL solution for injection
LOVENOX (and associated names) 12,000 IU (120 mg)/0.8 mL solution for injection
LOVENOX (and associated names) 15,000 IU (150 mg)/1 mL solution for injection

Enoxaparin

[See Annex I - To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe (0.2 mL) contains 2,000 IU (20 mg) enoxaparin sodium
One pre-filled syringe (0.4 mL) contains 4,000 IU (40 mg) enoxaparin sodium
One pre-filled syringe (0.6 mL) contains 6,000 IU (60 mg) enoxaparin sodium
One pre-filled syringe (0.8 mL) contains 8,000 IU (80 mg) enoxaparin sodium
One pre-filled syringe (0.8 mL) contains 12,000 IU (120 mg) enoxaparin sodium
One pre-filled syringe (1 mL) contains 10,000 IU (100 mg) enoxaparin sodium
One pre-filled syringe (1 mL) contains 15,000 IU (150 mg) enoxaparin sodium

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

[To be completed nationally]

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

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

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

LOVENOX (and associated names) 2,000 IU (20 mg)/0.2 mL solution for injection
LOVENOX (and associated names) 4,000 IU (40 mg)/0.4 mL solution for injection
LOVENOX (and associated names) 6,000 IU (60 mg)/0.6 mL solution for injection
LOVENOX (and associated names) 8,000 IU (80 mg)/0.8 mL solution for injection
LOVENOX (and associated names) 10,000 IU (100 mg)/1 mL solution for injection
LOVENOX (and associated names) 12,000 IU (120 mg)/0.8 mL solution for injection
LOVENOX (and associated names) 15,000 IU (150 mg)/1 mL solution for injection
[See Annex I - To be completed nationally]

enoxaparin

2. METHOD OF ADMINISTRATION

SC/ IV

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX AMPOULE

1. NAME OF THE MEDICINAL PRODUCT

LOVENOX (and associated names) 10,000 IU (100 mg)/1 mL solution for injection

[See Annex I - To be completed nationally]

Enoxaparin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ampoule (1 mL) contains 10,000 IU (100 mg) enoxaparin sodium

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
[To be completed nationally]

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

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
[See Annex I - To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE

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

LOVENOX (and associated names) 10,000 IU (100 mg)/1 mL solution for injection

[See Annex I - To be completed nationally]

enoxaparin

2. METHOD OF ADMINISTRATION

SC/ IV

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX MULTIDOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

LOVENOX (and associated names) 30,000 IU (300 mg)/3 mL solution for injection
LOVENOX (and associated names) 50,000 IU (500 mg)/5 mL solution for injection
LOVENOX (and associated names) 100,000 IU (1,000 mg)/10 mL solution for injection

[See Annex I - To be completed nationally]

Enoxaparin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial (3.0 mL) contains 30,000 IU (300 mg) enoxaparin sodium
One vial (5.0 mL) contains 50,000 IU (500 mg) enoxaparin sodium
One vial (10.0 mL) contains 100,000 IU (1,000 mg) enoxaparin sodium

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

[To be completed nationally]

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

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
[See Annex I - To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

MULTIPLE DOSE VIALS

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

LOVENOX (and associated names) 30,000 IU (300 mg) /3.0 mL solution for injection
LOVENOX (and associated names) 50,000 IU (500 mg)/5.0 mL solution for injection
LOVENOX (and associated names) 100,000 IU (1,000 mg)/10 mL solution for injection
[See Annex I - To be completed nationally]

enoxaparin

2. METHOD OF ADMINISTRATION

SC / IV

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX 10,000 IU/10 mL (100 mg/10 mL) VIAL

1. NAME OF THE MEDICINAL PRODUCT

LOVENOX (and associated names) 10,000 IU (100 mg)/10 mL solution for injection
[See Annex I - To be completed nationally]

Enoxaparin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial (10.0 mL) contains 10,000 IU (100 mg) enoxaparin sodium.

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before 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

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
[See Annex I - To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10,000 IU/10 mL (100 mg/10 mL) VIAL

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

LOVENOX (and associated names) 10,000 IU (100 mg)/10 mL solution for injection
[See Annex I - To be completed nationally]

enoxaparin

2. METHOD OF ADMINISTRATION

Extracorporeal use

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON PEN

1. NAME OF THE MEDICINAL PRODUCT

LOVENOX 10 x 4,000 IU (10 x 40 mg) Pen
Enoxaparin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pen contains 3.0 mL corresponding to 10 single doses of 4,000 IU (40 mg) enoxaparin sodium.

3. LIST OF EXCIPIENTS

[to be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

[to be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[to be completed nationally]

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

[to be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

[to be completed nationally]

16. INFORMATION IN BRAILLE

LOVENOX 10 x 4,000 IU (10 x 40 mg) Pen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN

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

LOVENOX 10 x 4,000 IU (10 x 40 mg) Pen
enoxaparin

2. METHOD OF ADMINISTRATION

SC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.0 mL

6. OTHER

1. taking on ……
at …….. ….

0 1 2 3 4 5 6 7 8 9 10

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↕
L

[to be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the user

LOVENOX (and associated names) 2,000 IU (20 mg)/0.2 mL solution for injection
LOVENOX (and associated names) 4,000 IU (40 mg)/0.4 mL solution for injection
LOVENOX (and associated names) 6,000 IU (60 mg)/0.6 mL solution for injection
LOVENOX (and associated names) 8,000 IU (80 mg)/0.8 mL solution for injection
LOVENOX (and associated names) 10,000 IU (100 mg)/1 mL solution for injection
LOVENOX (and associated names) 30,000 IU (300 mg)/3 mL solution for injection
LOVENOX(and associated names) 50,000 IU (500 mg)/5 mL solution for injection
LOVENOX(and associated names) 100,000 IU (1,000 mg)/10 mL solution for injection
LOVENOX (and associated names) 12,000 IU (120 mg)/0.8 mL solution for injection
LOVENOX (and associated names) 15,000 IU (150 mg)/1 mL solution for injection

[See Annex I - To be completed nationally]

enoxaparin sodium

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 or 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LOVENOX (and associated names) is and what it is used for

LOVENOX (and associated names) contains the active substance called enoxaparin sodium that is a low molecular weight heparin (LMWH).

LOVENOX (and associated names) 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 blood clots from forming in your blood.

LOVENOX (and associated names) 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 an acute illness and face period of limited mobility
    - When you have unstable angina (a condition when not enough blood gets to your heart)
    - After a heart attack

- Stop blood clots 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 (and associated names)

Do not use LOVENOX (and associated names)

- If you are allergic to enoxaparin sodium or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction include: rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- If you are allergic to heparin or other low molecular weight heparins such as nadroparin, tinzaparin or dalteparin.
- If you have had a reaction to heparin that caused a severe drop in the number of your clotting cells (platelets) - this reaction is called heparin-induced thrombocytopenia - within the last 100 days or if you have antibodies against enoxaparin in your blood.
- If 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), including recent bleeding stroke.
- If you are using LOVENOX (and associated names) to treat blood clots in your body and going to receive spinal or epidural anaesthesia or lumbar puncture within 24 hours.

multiple dose vial containing benzyl alcohol:

- If the patient is a premature or newborn baby up to 1 month because of the risk of severe toxicity including abnormal respiration ("gasping syndrome").

Warnings and precautions

LOVENOX (and associated names) should not be used interchangeably with other medicines belonging to the group of low molecular weight heparins. 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 (and associated names) if:

- you have ever had a reaction to heparin that caused a severe drop in the number of your platelets
- you are going to receive spinal or epidural anesthesia or lumbar puncture (see Operations and Anaesthetics): a delay should be respected between Lovenox use and this procedure.
- you have had a heart valve fitted
- you have endocarditis (an infection of the inner lining of the heart)
- you have 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 level of potassium in your blood (this may be checked with a blood test)
- are currently using medicines which affect bleeding (see section below – Other medicines.

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.

Other medicines and LOVENOX (and associated names)

Tell your doctor or pharmacist if you are taking or might take/use 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 also in section 3, “Changing of anticoagulant medicine”)
- 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 level in your blood such as potassium salts, water pills, some medicines for heart problems.

Operations and Anaesthetics
If you are going to have a spinal puncture or an operation where an epidural or spinal anaesthetic is used, tell you doctor that you are using LOVENOX (and associated names). See “Do not use LOVENOX (and associated names)”. Also, tell your doctor if you have any problem with your spine or if you ever had spinal surgery.

Pregnancy and breastfeeding
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 for advice before taking this medicine.

Multiple dose vial containing benzyl alcohol:
Important information about some of the ingredients of LOVENOX (and associated names)
LOVENOX (and associated names) contains benzyl alcohol [benzyl alcohol content to be completed nationally]. This is a preservative. It may cause toxic and allergic reactions in infants up to 3 years old. It must not be used in premature babies or babies up to 1 month old due to the risk risk of severe toxicity including abnormal respiration.
It is recommended to use the LOVENOX formulation without benzyl alcohol in pregnant women.

Driving and using machines
LOVENOX (and associated names) 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.

3. How to use LOVENOX (and associated names)
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 (and associated names). This is because it needs to be given as an injection.
- When you go home, you may need to continue to use LOVENOX (and associated names) and give it yourself (see instructions below on how to do this).
- LOVENOX (and associated names) is usually given by injection underneath the skin (subcutaneous).
- LOVENOX (and associated names) can be given by injection into your vein (intravenous) after certain types of heart attack or operation.

- LOVENOX (and associated names) can be added to the tube leaving the body (arterial line) at the start of the dialysis session.

Do not inject LOVENOX (and associated names) into a muscle.

How much will be given to you

- Your doctor will decide how much LOVENOX (and associated names) 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 (and associated names).

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 (and associated names).

2. Stopping blood clots forming in your blood in the following situations:

❖*Operation 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 (and associated names) each day.
- If you are going to have an operation your first injection will be usually 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 (and associated names) each day.
- Your doctor will decide how long you should receive LOVENOX (and associated names).

❖*After you have had a heart attack*

LOVENOX (and associated names) can be used for two different types of heart attack called STEMI (ST segment elevation myocardial infarction) or Non STEMI (NSTEMI). The amount of LOVENOX (and associated names) given to you will depend on your age and the kind of heart attack you have had.

NSTEMI 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 (and associated names).

STEMI type of heart attack if you are under 75 years old:

- An initial dose of 3,000 IU (30 mg) of LOVENOX (and associated names) will be given as injection into your vein.
- At the same time you will also be given LOVENOX (and associated names) 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 (and associated names).

STEMI 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 (and associated names) given for the first two injections is 7,500 IU (75 mg).
- Your doctor will decide how long you should receive LOVENOX (and associated names).

For patients have an operation called percutaneous coronary intervention (PCI):
Depending on when you were last given LOVENOX (and associated names), your doctor may decide to give an additional dose of LOVENOX (and associated names) before a PCI operation. This is by injection into your vein.

3. 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 (and associated names) 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 futher dose of 50 IU to 100 IU (0.5 to 1 mg) for every kilogram of your weight, if necessary.

For prefilled syringe PL: Instruction for use of the syringe [To be completed locally]

Changing of anticoagulant treatment
- *Changing from LOVENOX (and associated names) to blood thinners called vitamin-K antagonists (e.g. warfarin)*
  Your doctor will request you perform blood tests called INR and tell you when to stop LOVENOX (and associated names) accordingly.

- *Changing from blood thinners called vitamin-K antagonists (e.g. warfarin) to LOVENOX (and associated names)*
  Stop taking the vitamin-K antagonist. Your doctor will request you perform blood tests called INR and tell you when to start LOVENOX (and associated names) accordingly.

- *Changing from LOVENOX (and associated names) to treatment with direct oral anticoagulant*
  Stop taking LOVENOX (and associated names). 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 (and associated names)*
  Stop taking direct oral anticoagulant. Do not start treatment with LOVENOX (and associated names) until 12 hours after the final dose of direct oral anticoagulant.

Use in children and adolescents
The safety and efficacy of LOVENOX (and associated names) has not been evaluated in children or adolescents.

If you use more LOVENOX (and associated names) than you should
If you think that you have used too much or too little LOVENOX (and associated names), tell your doctor, nurse or pharmacist immediately, even if you have no signs of a problem. If a child accidentally injects or swallows LOVENOX (and associated names), take them to a hospital causualty department straight away.

If you forget to use LOVENOX (and associated names)
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 (and associated names)
If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse. It is important for you to keep having LOVENOX (and associated names) injections until your doctor decides to stop them. If you stop, you could get a blood clot which can be very dangerous.

4. Possible side effects

Like other similar medicines (medicines to reduce blood clotting), LOVENOX (and associated names) may cause bleeding which may potentially be life-threatening. In some cases the bleeding may not be obvious.

If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling), consult your doctor immediately.
Your doctor may decide to keep you under closer observation or change your medicine.

Stop using LOVENOX (and associated names) and talk to a doctor or nurse at once if you get any signs of a severe allergic reaction (such as difficulty breathing, swelling of the lips, mouth, throat or eyes).

You should tell 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.

Overall list of possible 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 (and associated names).
- Skin rash (hives, urticaria).
- 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).
- You notice yellowing of your skin or eyes and your urine becomes darker in colour. 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 anaesthetic.
- Lost 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 orpharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LOVENOX (and associated names)

[To be completed nationally]

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 {description of the visible signs of deterioration}.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What LOVENOX (and associated names) contains

- The active substance(s) is enoxaparin sodium

[To be completed nationally]

What LOVENOX (and associated names) looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]
[See Annex I - To be completed nationally] *[For referral procedures]*

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

{Name of the Member State} {Name of the medicinal product}
{Name of the Member State} {Name of the medicinal product}

[See Annex I - To be completed nationally] *[For referral procedures, as appropriate]*

This leaflet was last revised in {MM/YYYY} {month YYYY}.

[To be completed nationally]

Other sources of information

Detailed information on this medicine is available on the website of {name of MS Agency (link)}

Package leaflet: Information for the user

LOVENOX (and associated names) 10,000 IU (100 mg)/10 mL solution for injection
[See Annex I - To be completed nationally]

enoxaparin sodium

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 or 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LOVENOX (and associated names) is and what it is used for

LOVENOX (and associated names) contains the active substance called enoxaparin sodium that is a low molecular weight heparin (LMWH).

LOVENOX (and associated names) 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 blood clots from forming in your blood.

LOVENOX (and associated names) 10,000 IU (100 mg)/10 mL is used to stop blood clots 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 (and associated names)

Do not use LOVENOX (and associated names)
- If you are allergic to enoxaparin sodium or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction include: rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- If you are allergic to heparin or other low molecular weight heparins such as nadroparin, tinzaparin or dalteparin.
- If you have had a reaction to heparin that caused a severe drop in the number of your clotting cells (platelets) - this reaction is called heparin-induced thrombocytopenia - within the last 100 days or if you have antibodies against enoxaparin in you blood.
- If 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), including recent bleeding stroke.
- If you are using LOVENOX (and associated names) to treat blood clots in your body and going to receive spinal or epidural anaesthesia or lumbar puncture within 24 hours.

Warnings and precautions
LOVENOX (and associated names) should not be used interchangeably with other medicines belonging to the group of LMWHs. 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 (and associated names) if:

- you have ever had a reaction to heparin that caused a severe drop in the number of your platelets
- you are going to receive spinal or epidural anesthesia or lumbar puncture (see Operations and Anaesthetics): a delay should be respected between Lovenox use and this procedure.
- you have had a heart valve fitted
- you have endocarditis (an infection of the inner lining of the heart)
- you have 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 liver problems
- you are underweight or overweight
- you have high level of potassium in your blood (this may be checked with a blood test)
- are currently using medicines which affect bleeding (see section below – "Other medicines").

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.

Other medicines and LOVENOX (and associated names)
Tell your doctor or pharmacist if you are taking or might take/use 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
- 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 level in your blood such as potassium salts, water pills, some medicines for heart problems.

Operations and Anaesthetics
If you are going to have a spinal puncture or an operation where an epidural or spinal anaesthetic is used, tell you doctor that you are using LOVENOX (and associated names) . See "Do not use LOVENOX (and associated names)". Also, tell your doctor if you have any problem with your spine or if you ever had spinal surgery.

Pregnancy and breastfeeding
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 for advice before taking this medicine.

Driving and using machines
LOVENOX (and associated names) 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.

3. How to use LOVENOX (and associated names)

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 (and associated names). This is because it needs to be given as an injection.
- LOVENOX (and associated names) is added to the tube leaving the body (arterial line) at the start of the dialysis session.

Do not inject LOVENOX (and associated names) into a muscle.

How much will be given to you
Your doctor will decide how much LOVENOX (and associated names) to give you.
The usual dose is 100 IU (1 mg) for every kilogram of your weight.
This amount is usually enough for a 4-hour session. However, your doctor may give you a futher dose of 50 IU to 100 IU (0.5 to 1 mg) for every kilogram of your weight, if necessary.

Use in children and adolescents
The safety and efficacy of LOVENOX (and associated names) has not been evaluated in children or adolescents.

If you receive more LOVENOX (and associated names) than you should
If you think that you have received too much or too little LOVENOX (and associated names), tell your doctor, nurse or pharmacist immediately, even if you have no signs of a problem. If a child accidentally injects or swallows LOVENOX (and associated names), take them to a hospital causualty department straight away.

4. Possible side effects

Like other similar medicines (medicines to reduce blood clotting), LOVENOX (and associated names) may cause bleeding which may potentially be life-threatening. In some cases the bleeding may not be obvious.

If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling), consult your doctor immediately.
Your doctor may decide to keep you under closer observation or change your medicine.

Stop using LOVENOX (and associated names) and talk to a doctor or nurse at once if you get any signs of a severe allergic reaction (such as difficulty breathing, swelling of the lips, mouth, throat or eyes).

You should tell 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.

Overall list of possible 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 (and associated names).
- Skin rash (hives, urticaria).
- 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).
- You notice yellowing of your skin or eyes and your urine becomes darker in colour. 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 anaesthetic.
- Lost 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 orpharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LOVENOX (and associated names)

[To be completed nationally]

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 {description of the visible signs of deterioration}.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What LOVENOX (and associated names) contains

- The active substance(s) is enoxaparin sodium

[To be completed nationally]

What LOVENOX (and associated names) looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]
[See Annex I - To be completed nationally] *[For referral procedures]*

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

{Name of the Member State} {Name of the medicinal product}
{Name of the Member State} {Name of the medicinal product}

[See Annex I - To be completed nationally] *[For referral procedures, as appropriate]*

This leaflet was last revised in {MM/YYYY} {month YYYY}.

[To be completed nationally]

Other sources of information

Detailed information on this medicine is available on the website of {name of MS Agency (link)}

Package leaflet: Information for the user

LOVENOX (and associated names) 10 x 4,000 IU (10 x 40 mg) doses solution for injection in a pen

[See Annex I - To be completed nationally]

enoxaparin sodium

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 or 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LOVENOX (and associated names) is and what it is used for

LOVENOX (and associated names) contains the active substance called enoxaparin sodium that is a low molecular weight heparin (LMWH).

LOVENOX (and associated names) 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 blood clots from forming in your blood.

LOVENOX (and associated names) in a pen 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 an acute illness and face period of limited mobility
    - When you have unstable angina (a condition when not enough blood gets to your heart)
    - After a heart attack

2. What you need to know before you use LOVENOX (and associated names)

Do not use LOVENOX (and associated names)
- If you are allergic to enoxaparin sodium or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction include: rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.

- If you are allergic to heparin or other low molecular weight heparins such as nadroparin, tinzaparin or dalteparin.
- If you have had a reaction to heparin that caused a severe drop in the number of your clotting cells (platelets) - this reaction is called heparin-induced thrombocytopenia - within the last 100 days or if you have antibodies against enoxaparin in you blood.
- If 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), including recent bleeding stroke.
- If you are using LOVENOX (and associated names) to treat blood clots in your body and going to receive spinal or epidural anaesthesia or lumbar puncture within 24 hours.
- If the patient is a premature or newborn baby up to 1 month because of the risk of severe toxicity including abnormal respiration ("gasping syndrome").

Warnings and precautions
LOVENOX (and associated names) should not be used interchangeably with other medicines belonging to the group of low molecular weight heparins. 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 (and associated names) if:
- you have ever had a reaction to heparin that caused a severe drop in the number of your platelets
- you are going to receive spinal or epidural anesthesia or lumbar puncture (see Operations and Anaesthetics): a delay should be respected between Lovenox use and this procedure.
- you have had a heart valve fitted
- you have history of gastric ulcer
- you have endocarditis (an infection of the inner lining of the heart)
- 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 level of potassium in your blood (this may be checked with a blood test)
- are currently using medicines which affect bleeding (see section below – "Other medicines").

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.

Other medicines and LOVENOX (and associated names)
Tell your doctor or pharmacist if you are taking or might take/use 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 also in section 3, "Changing of anticoagulant medicine")
- 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 level in your blood such as potassium salts, water pills, some medicines for heart problems.

Operations and Anaesthetics
If you are going to have a spinal puncture or an operation where an epidural or spinal anaesthetic is used, tell you doctor that you are using LOVENOX (and associated names). See "Do not use LOVENOX (and associated names)". Also, tell your doctor if you have any problem with your spine or if you ever had spinal surgery.

Pregnancy and breastfeeding
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 for advice before taking this medicine.

Important information about some of the ingredients of LOVENOX (and associated names)
LOVENOX (and associated names) contains benzyl alcohol [benzyl alcohol content to be completed nationally]. This is a preservative. It may cause toxic and allergic reactions in infants up to 3 years old. It must not be used in premature babies or babies up to 1 month old due to the risk of severe toxicity including abnormal respiration.
It is recommended to use the LOVENOX formulation without benzyl alcohol in pregnant women.

Driving and using machines
LOVENOX (and associated names) 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.

3. How to use LOVENOX (and associated names)
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
- LOVENOX (and associated names) is usually given by injection underneath the skin (subcutaneous).
- When you go home, you may need to continue to use LOVENOX (and associated names) and give it yourself (see instructions below on how to do this).

Do not inject LOVENOX (and associated names) into a muscle.

How much will be given to you
- Your doctor will decide how much LOVENOX (and associated names) 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 (and associated names).

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 (and associated names).

2. Stopping blood clots forming in your blood in the following situations:

❖*Operation 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 (and associated names) each day.
- If you are going to have an operation your first injection will be usually 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 (and associated names) each day.
- Your doctor will decide how long you should receive LOVENOX (and associated names).

❖*After you have had a heart attack*

LOVENOX (and associated names) can be used for two different types of heart attack called STEMI (ST segment elevation myocardial infarction) or Non–STEMI (NSTEMI). The amount of LOVENOX (and associated names) given to you will depend on your age and the kind of heart attack you have had.

NSTEMI 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 (and associated names).

STEMI type of heart attack if you are under 75 years old:

- An initial dose of 3,000 IU (30 mg) of LOVENOX (and associated names) will be given as injection into your vein.
- At the same time you will also be given LOVENOX (and associated names) 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 (and associated names).

STEMI 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 (and associated names) given for the first two injections is 7,500 IU (75 mg).
- Your doctor will decide how long you should receive LOVENOX (and associated names).

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

Depending on when you were last given LOVENOX (and associated names), your doctor may decide to give an additional dose of LOVENOX (and associated names) before a PCI operation. This is by injection into your vein.

Instruction for use of the pen [To be completed locally]

Changing of anticoagulant treatment

- *Changing from LOVENOX (and associated names) to blood thinners called vitamin-K antagonists (e.g. warfarin)*
  Your doctor will request you perform blood tests called INR and tell you when to stop LOVENOX (and associated names) accordingly.

- *Changing from blood thinners called vitamin-K antagonists (e.g. warfarin) to LOVENOX (and associated names)*
  Stop taking the vitamin-K antagonist. Your doctor will request you perform blood tests called INR and tell you when to start LOVENOX (and associated names) accordingly.

- *Changing from LOVENOX (and associated names) to treatment with direct oral anticoagulant*
  Stop taking LOVENOX (and associated names). 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 (and associated names)*
  Stop taking direct oral anticoagulant. Do not start treatment with LOVENOX (and associated names) until 12 hours after the final dose of direct oral anticoagulant.

Use in children and adolescents
The safety and efficacy of LOVENOX (and associated names) has not been evaluated in children or adolescents.

If you use more LOVENOX (and associated names) than you should
If you think that you have used too much or too little LOVENOX (and associated names), tell your doctor, nurse or pharmacist immediately, even if you have no signs of a problem. If a child accidentally injects or swallows LOVENOX (and associated names), take them to a hospital causualty department straight away.

If you forget to use LOVENOX (and associated names)
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 (and associated names)
If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse. It is important for you to keep having LOVENOX (and associated names) injections until your doctor decides to stop them. If you stop, you could get a blood clot which can be very dangerous.

4. Possible side effects

Like other similar medicines (medicines to reduce blood clotting), LOVENOX (and associated names) may cause bleeding which may potentially be life-threatening. In some cases the bleeding may not be obvious.

If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling), consult your doctor immediately.
Your doctor may decide to keep you under closer observation or change your medicine.

Stop using LOVENOX (and associated names) and talk to a doctor or nurse at once if you get any signs of a severe allergic reaction (such as difficulty breathing, swelling of the lips, mouth, throat or eyes).

You should tell 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.

Overall list of possible 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 (and associated names).
- Skin rash (hives, urticaria).
- 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).
- You notice yellowing of your skin or eyes and your urine becomes darker in colour. 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 anaesthetic.
- Lost 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 orpharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LOVENOX (and associated names)

[To be completed nationally]

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 {description of the visible signs of deterioration}.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What LOVENOX (and associated names) contains

- The active substance(s) is enoxaparin sodium

[To be completed nationally]

What LOVENOX (and associated names) looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]
[See Annex I - To be completed nationally] *[For referral procedures]*

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

{Name of the Member State} {Name of the medicinal product}
{Name of the Member State} {Name of the medicinal product}

[See Annex I - To be completed nationally] *[For referral procedures, as appropriate]*

This leaflet was last revised in {MM/YYYY} {month YYYY}.

[To be completed nationally]

Other sources of information

Detailed information on this medicine is available on the website of {name of MS Agency (link)}