Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ghemaxan 12,000 IU (120 mg)/0.8 mL solution for injection in pre-filled syringes

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains enoxaparin sodium 12,000 IU anti-Xa activity (equivalent to 120 mg) in 0.8 mL water for injections.

For the full list of excipients, see section 6.1.

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

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ghemaxan 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.
- Extended treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of its recurrence in patients with active cancer.
- Prevention of thrombus formation in the extracorporeal 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 a 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 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, 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, 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 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 a twice-daily injection 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).

In the extended treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of its recurrence in patients with active cancer, physicians should carefully assess the individual thromboembolic and bleeding risks of the patient. The recommended dose is 100 IU/kg (1 mg/kg) administered twice daily by SC injections for 5 to 10 days, followed by a 150 IU/kg (1.5 mg/kg) once daily SC injection up to 6 months. The benefit of continuous anticoagulant therapy should be reassessed after 6 months of treatment.

Prevention of thrombus formation during 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 stabilisation. 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-naïve 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 the paediatric population have not been established.

Elderly
For all indications except STEMI, no dose reduction is necessary in 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 exercised 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 extracorporeal 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
Extended treatment of DVT and PE in patients with active cancer	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of unstable angina and NSTEMI	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of acute STEMI (patients under 75 years) Treatment of acute STEMI (patients over 75 years)	1 × 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 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 dosage 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
Ghemaxan should not be administered by the intramuscular route.

For the prophylaxis of venous thromboembolic disease following surgery, treatment of DVT and PE, extended treatment of DVT and PE in patients with active cancer, treatment of unstable angina and NSTEMI, enoxaparin sodium should be administered by SC injection.

• For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection.

• For the prevention of thrombus formation in the extracorporeal circulation during haemodialysis, it is administered through the arterial line of a dialysis circuit.

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

- SC injection technique

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

Do not expel the air bubble from the syringe before the injection to avoid the loss of medicinal product when using pre-filled syringes. When the quantity of medicinal product to be injected needs adjusting 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 cases, the volume shall be rounded up to the nearest graduation.

Administration should be alternated between the left and right anterolateral or posterolateral abdominal wall. The whole length of the needle should be introduced vertically into a skin fold held between the thumb and index finger. The skin fold should not be released until the injection is complete. Do not rub the injection site after administration.

Note that for the pre-filled syringes equipped with a needle shield guard, the safety system is triggered at the end of the injection (see instructions in section 6.6).

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

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

For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection. For IV injection, either the multidose vial or pre-filled syringe can be used. Enoxaparin sodium should be administered through an IV line. It should not be mixed or co-administered with other medicinal products. To avoid the possible mixture of enoxaparin sodium with all other medicinal products, 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 medicinal product. 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 excess 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 an injection site in the intravenous line.

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

For patients being managed with 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 medicinal product 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) × 0.1] or using the table below. It is recommended that the dilution be prepared

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 extracorporeal 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 Normalised 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 of 15-30 mL/min, consider doubling the timing of puncture/catheter placement or removal to at least 24 hours.
The 2-hour 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 of 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 haematoma 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).

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-II 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 for several years.

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

- *Monitoring of platelet counts*

In patients with cancer with a platelet count below 80 G/L, anticoagulation treatment can only be considered on a case-by-case basis and careful monitoring is recommended.
The risk of antibody-mediated HIT also exists with LMWHs. Should thrombocytopenia occur, it usually appears between the 5th

and 21st day after the start of enoxaparin sodium treatment.
The risk of HIT is higher in post-operative patients and mainly after cardiac surgery and in patients with cancer.
Therefore, it is recommended that platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during 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), the 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 in 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 ischaemic stroke,
- severe arterial hypertension,
- recent diabetic retinopathy,
- neuro- or ophthalmologic surgery,
- concomitant use of medicinal products 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 are therefore 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 of 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 medicinal products 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 and 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 of 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 performed to detect any signs and symptoms of neurological impairment, such as

midline back pain, sensory and motor deficits (numbness or weakness in lower limbs) or 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 haematoma 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 revascularisation procedures*

To minimise the risk of bleeding following 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 homeostasis at the puncture site after PCI. If a closure device is used, the sheath can be removed immediately. If a manual compression method is used, the sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or haematoma formation.

- *Acute infective endocarditis*

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

- *Mechanical prosthetic heart valves*

The use of enoxaparin sodium has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. 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 diseases 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 out 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 within the prophylactic dosage ranges. Elderly patients (especially patients eighty years of age and older) may be at increased risk for bleeding complications within 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 to 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 extracorporeal circulation during haemodialysis
In patients with severe renal impairment (creatinine clearance 15-30 mL/min), since exposure to 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 to enoxaparin sodium at the prophylactic dosage (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients (see section 5.2).

- *Obese patients*

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI > 30 kg/m^2) have not been fully established 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 and those 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 LMWH traceability, it is recommended that healthcare professionals record the trade name and batch number of the administered product in the patient's file.

- *Sodium content*

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

- *Acute generalized exanthematous pustulosis*

Acute generalized exanthematous pustulosis (AGEP) has been reported with frequency not known in association with enoxaparin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, enoxaparin should be withdrawn immediately and an alternative treatment considered (as appropriate).

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 an 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 epidural anaesthesia is planned, it is recommended that enoxaparin sodium treatment be withdrawn beforehand (see section 4.4).

Breastfeeding
It is unknown whether unchanged enoxaparin is excreted in human milk. In lactating rats, the passage of enoxaparin or its metabolites in milk is very low. The oral absorption of enoxaparin sodium is unlikely. Ghemaxan 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, performed with a reference product. 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.

The enoxaparin sodium regimen administered during these clinical trials varies depending on the indication. 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, the 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).

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

Acute generalized exanthematous pustulosis (AGEP) has been reported in association with enoxaparin treatment (see section 4.4).

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); very rare (<1/10,000) or not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

- Common: haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis
- Rare: eosinophilia*
- Rare: cases of immuno-allergic thrombocytopenia with thrombosis; in some of these, 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).

Hepatobiliary disorders

- Very common: hepatic enzymes increased (mainly transaminases > 3 times the upper limit of normal)
- Uncommon: hepatocellular liver injury *
- Rare: cholestatic liver injury*

Skin and subcutaneous tissue disorders

- Common: urticaria, pruritus, erythema
- Uncommon: bullous dermatitis
- Rare: alopecia*
- Rare: cutaneous vasculitis*, skin necrosis* usually occurring at the injection site (these phenomena have usually been preceded by purpura or erythematous plaques, infiltrated and painful).

Injection site nodules* (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.

- Not known: Acute generalized exanthematous pustulosis (AGEP)

Musculoskeletal and connective tissue disorders

- Rare: osteoporosis* following long-term therapy (longer 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 medicinal products 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**	**Extended treatment of DVT and PE in patients with active cancer**	**Treatment in patients with unstable angina and non-Q-wave MI**	**Treatment in patients with acute STEMI**
Blood and lymphatic system disorders	*Very common*: Haemorrhage [α] *Rare:* Retroperitoneal haemorrhage	*Common:* Haemorrhage [α]	*Very common:* Haemorrhage [α] *Uncommon:* Intracranial haemorrhage, retroperitoneal haemorrhage	*Common [β]:* 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 gastrointestinal haemorrhage.

[β]: frequency based on a retrospective study on a registry including 3526 patients (see section 5.1)

Thrombocytopenia and thrombocytosis

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

						thrombocytopenia

*: Platelets 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 neutralised by the slow IV injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected; 1 mg protamine neutralises 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 more 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 neutralised (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, such as 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 hospitalised, with enoxaparin sodium 4,000 IU (40 mg) SC, were randomised 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 hospitalised, with enoxaparin sodium 4,000 IU (40 mg) SC were randomised 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, multicentre 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, multicentre, 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 metres 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 was 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 multicentre, parallel-group study, 900 patients with acute lower extremity DVT with or without PE were randomised 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 randomised 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	298 (100)	312 (100)	290 (100)
Patients with or without PE			
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 was 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, respectively.

Extendedtreatmentofdeepveinthrombosis(DVT)andpulmonaryembolism(PE)andpreventionofits recurrence in patients with active cancer
In clinical trials with limited number of patients, reported rates of recurrent VTE in patients treated with enoxaparin given once or twice daily for 3 to 6 months appear comparable to those with warfarin.

Effectiveness in real-life setting was assessed in a cohort of 4,451 patients with symptomatic VTE and active cancer from the multinational registry RIETE of patients with VTE and other thrombotic conditions. 3,526 patients received SC enoxaparin up to

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

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

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

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

Outcome N (%) (95%CI)	**Enoxaparin all regimens**	**Enoxaparinall regimens**					**EU-authorized LMWHs**
		Enoxaparin OD	**Enoxaparin BID**	**Enoxaparin BID to OD**	**Enoxaparin OD to BID**	**Enoxaparin More than one switch**	
	N=1432	N=444	N=529	N=406	N=14	N=39	N=428
	70	33	22	10	1	4	23
Recurrence	(4.9%)	(7.4%)	(4.2%)	(2.5%)	(7.1%)	(10.3%)	(5.4%)
of VTE	(3.8%-	(5.0%-	(2.5%-	(0.9%-	(0%-	(0.3%-	(3.2%-
	6.0%)	9.9%)	5.9%)	4.0%)	22.6%)	20.2%)	7.5%)
Major	111	31	52	21	1	6	18
bleeding	(7.8%)	(7.0%)	(9.8%)	(5.2%)	(7.1%)	(15.4%)	(4.2%)
(fatal and	(6.4%-	(4.6%-	(7.3%-	(3.0%-	(0%-	(3.5%-	(2.3%-
non-fatal)	9.1%)	9.4%)	12.4%)	7.3%)	22.6%)	27.2%)	6.1%)
Non-major	87	26	33	23	1	4	24
bleedings of	(6.1%)	(5.9%)	(6.2%)	(5.7%)	(7.1%)	(10.3%)	(5.6%)
clinical	(4.8%-	(3.7%-	(4.2%-	(3.4%-	(0%-	(0.3%-	(3.4%-
significance	7.3%)	8.0%)	8.3%)	7.9%)	22.6%)	20.2%)	7.8%)
	666	175	323	146	6	16	157
All-cause	(46.5%)	(39.4%)	(61.1%)	(36.0%)	(42.9%)	(41.0%)	(36.7%)
death	(43.9%-	(34.9%-	(56.9%-	(31.3%-	(13.2%-	(24.9%-	(32.1%-
	49.1%)	44.0%)	65.2%)	40.6%)	72.5%)	57.2%)	41.3%)
Fatal PE or	48	7	35	5	0 (0%)	1	11
fatal	(3.4%)	(1.6%)	(6.6%)	(1.2%)		(2.6%)	2.6%)
bleeding	(2.4%-	(0.4%-	(4.5%-	(0.2%-		(0%-	(1.1%-
related death	4.3%)	2.7%)	8.7%)	2.3%)		7.8%)	4.1%)
*All data with 95% CI							

Treatment of unstable angina and non ST elevation myocardial infarction

In a large multicentre study, 3,171 patients enrolled at the acute phase of unstable angina or non-Q-wave myocardial infarction were randomised 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 stabilisation, revascularisation 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 multicentre study, 20,479 patients with STEMI eligible to receive fibrinolytic therapy were randomised 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 a 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 endpoint, a composite of death from any cause or myocardial re-infarction in the first 30 days after randomisation [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 endpoint 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 for enoxaparin sodium, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomisation (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 endpoint 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 exercised 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).

Ghemaxan is a biosimilar medicinal product. Detailed information is available on the website of: Health Products Regulatory Authority (HPRA).

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, 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, 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 metabolised in the liver by desulfation and/or depolymerisation 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 no 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 to the 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 that, after a single SC 4,000 IU (40 mg) dose, 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

Water for injections

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).

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.
This medicinal product is for single use only. Discard any unused product.

6.5 Nature and contents of container

Solution for injection in a 0.5 mL or 1 mL Type I glass pre-filled syringe with staked needle and needle guard (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and plunger rod. The solution for injection is available in two different presentations:

1. The syringe is equipped with a needle guard
Ghemaxan 12,000 IU (120 mg)/0.8 mL solution for injection in pre-filled syringes:
packs of 2, 6 or 10 graduated pre-filled syringes and multipacks containing 30 (3 packs of 10) and 50 (5 packs of 10) graduated pre-filled syringes.

2. The syringe is not equipped with a needle guard
Ghemaxan 12,000 IU (120 mg)/0.8 mL solution for injection in pre-filled syringes:
packs of 10 graduated pre-filled syringes and multipack containing 30 (3 packs of 10) graduated pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The pre-filled syringe is ready for immediate use (see section 4.2).
For intravenous injection, the product can be diluted in normal saline (0.9%) or 5% dextrose in water.
The solution should be inspected visually prior to use. It must not be used if there is any change in the appearance of the solution.
The Ghemaxan pre-filled syringes are for single dose use only; discard any unused medicinal product.
Pre-filled syringes are supplied with or without a needle guard. The instructions for use are presented in the package leaflet.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

INSTRUCTIONS FOR USE: PRE-FILLED SYRINGE

How to give yourself an injection of Ghemaxan
If you are able to give Ghemaxan to yourself, your doctor or nurse will show you how to do this. Do not try to inject yourself if you have not been trained how to do so. If you are not sure what to do, talk to your doctor or nurse immediately.

Before injecting yourself with Ghemaxan
- Check the expiry date on the medicine. Do not use if the date has passed
- Check the syringe is not damaged and the medicine in it is a clear solution. If not, use another syringe
- Do not use this medicine if you notice any change in the appearance of the product.
- Make sure you know how much you are going to inject
- Check your abdomen to see if the last injection caused any redness, change in skin colour, swelling, oozing or is still painful, if so, talk to your doctor or nurse
- Decide where you are going to inject the medicine. Change the place where you inject each time from the right to the left side of your stomach. Ghemaxan should be injected just under the skin on your stomach, but not too near the belly button or any scar tissue (at least 5 cm away from these)

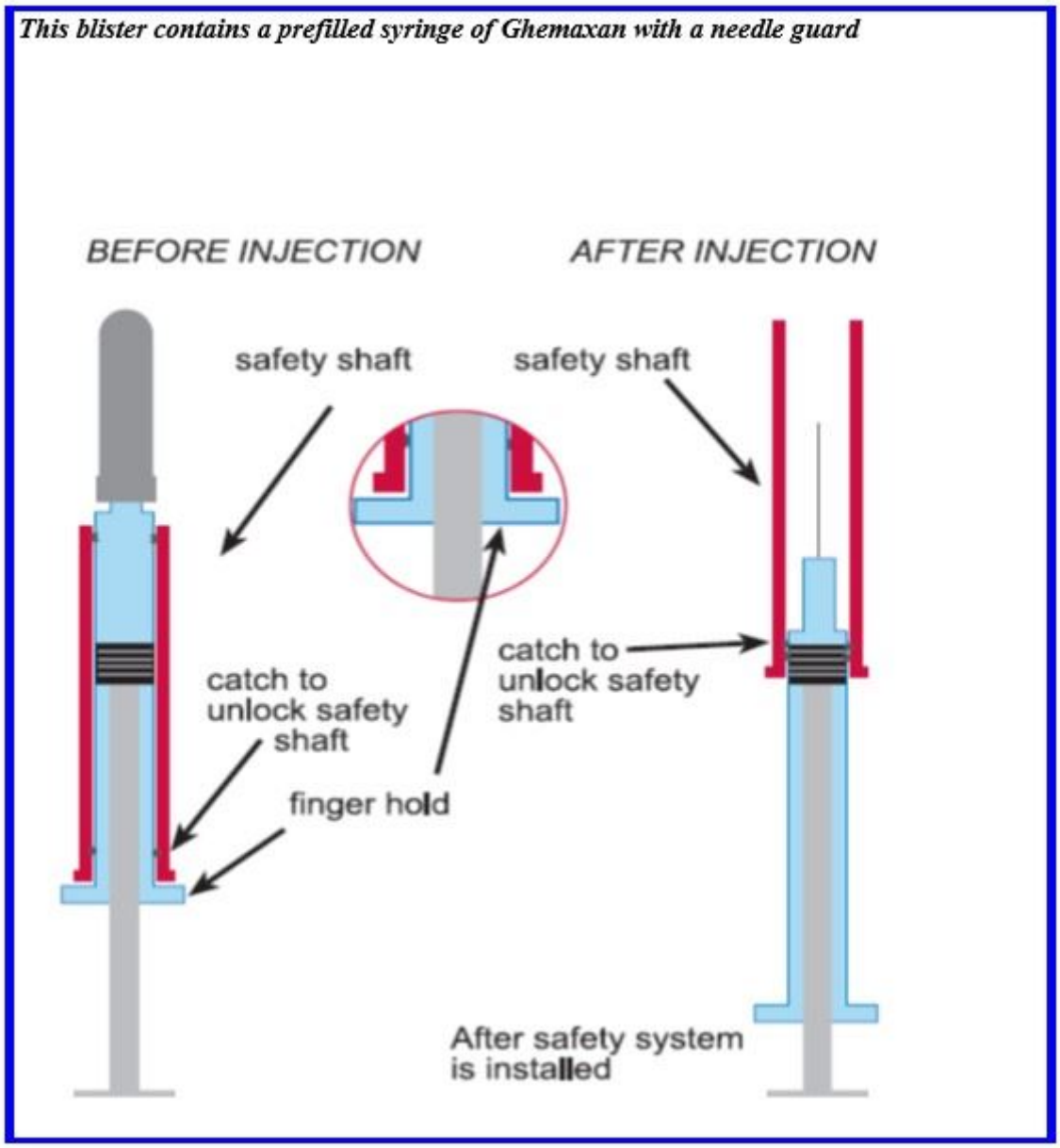
The pre-filled syringe is intended for single, one-time use only and are available in the following presentations:

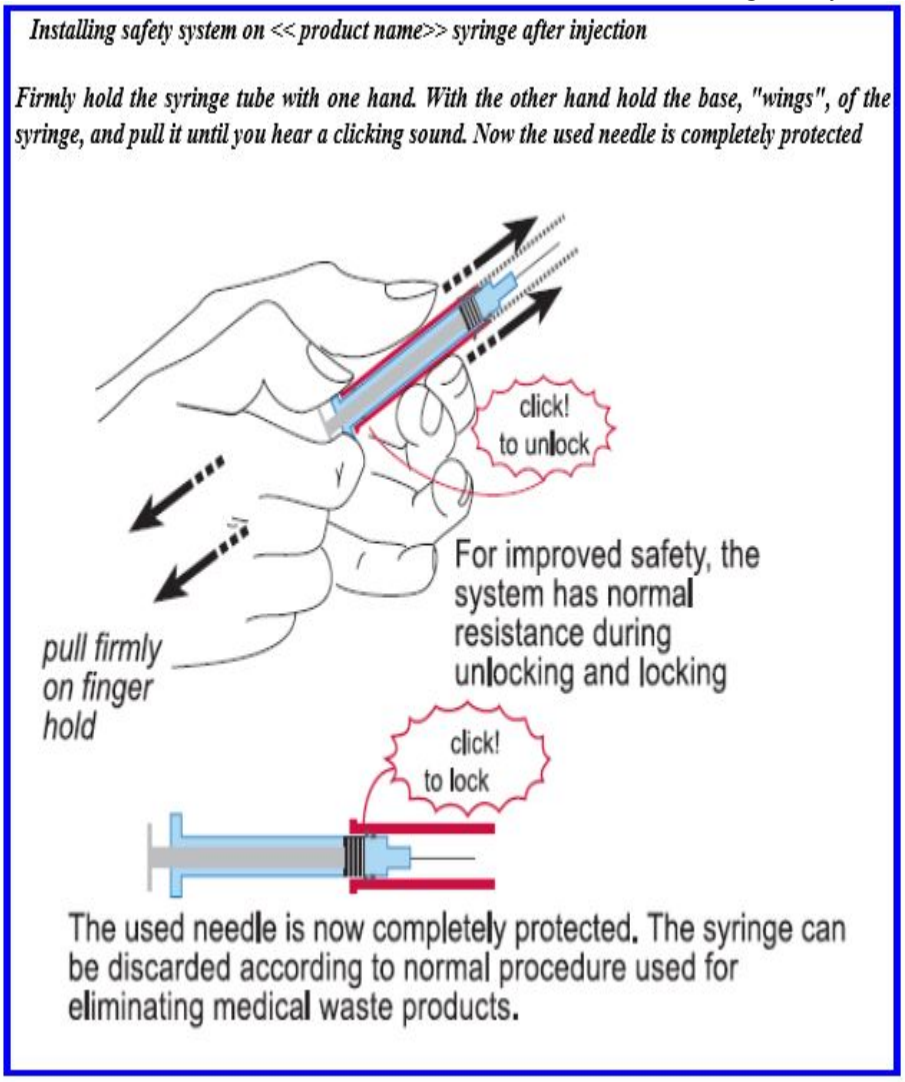
- with a needle guard
- without a needle guard

Instructions on injecting yourself with Ghemaxan:
You should be lying down and Ghemaxan administered by deep SC injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimise bruising, do not rub the injection site after completion of the injection.
Ghemaxan pre-filled syringes and graduated pre-filled syringes are for single, one-time use only. The syringes may be equipped with a needle guard; instructions for using syringes with this system are given below.
The safety shaft is provided with a catch to unlock and lock the system.

Remove the pre-filled syringe from the blister packaging by peeling at the arrow as directed on the blister. Do not remove by pulling on the plunger, as this may damage the syringe.

INSTRUCTIONS FOR USE: SAFETY DEVICE





7 MARKETING AUTHORISATION HOLDER

Chemi S.p.A.
Via dei Lavoratori, 54
Cinisello Balsamo (MI)
20092
Italy

8 MARKETING AUTHORISATION NUMBER

PA22937/001/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th June 2020
Date of last renewal: 7th March 2023

10 DATE OF REVISION OF THE TEXT

August 2025