SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clotinex 40 Pre Filled Syringe Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Pre-Filled Syringe (0.4 ml) contains Enoxaparin Sodium BP 40 mg equivalent to 4000 anti-Xa IU
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pre Filled Syringe Injection
Clotinex 40 Injection is a sterile solution of Enoxaparin Sodium in water for injection filled in graduated syringe with needle shield, orange color plunger rod and black plunger stopper. It is clear colorless transparent solution. Free from any visible foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- The prophylaxis of thromboembolic disorders of venous origin, in particular those which may be associated with orthopaedic or general surgery.
- The prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness.
- The treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both.
- The treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or
- with subsequent Percutaneous Coronary Intervention (PCI) in conjunction with thrombolytic drugs (fibrin or non-fibrin specific).
- The prevention of thrombus formation in the extracorporeal circulation during haemodialysis.

4.2 Posology and method of administration

Posology Adults:

Prophylaxis of venous thromboembolism:

In patients with a low to moderate risk of venous thromboembolism the recommended dosage is 20 mg (2,000 IU) once daily by subcutaneous injection for 7 to 10 days, or until the risk of thromboembolism has diminished. In patients undergoing surgery, the initial dose should be given approximately 2 hours pre-operatively. In patients with a higher risk, such as in orthopaedic surgery, the dosage should be 40 mg (4,000 IU) daily by subcutaneous injection with the initial dose administered approximately 12 hours before surgery.

Prophylaxis of venous thromboembolism in medical patients:

The recommended dose of enoxaparin sodium is 40 mg (4,000 IU) once daily by subcutaneous injection. Treatment with enoxaparin sodium is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days.

Treatment of venous thromboembolism:

Enoxaparin Sodium should be administered subcutaneously as a single daily injection of 1.5 mg/kg (150 IU/kg). Enoxaparin Sodium treatment is usually prescribed for at least 5 days and until adequate oral anticoagulation is established.

Dosage chart for 1.5mg/kg SC treatment of DVT, PE or both				
Patient weight	**Kg**	**Syringe label**	**Dose (mg)**	**Injection volume**
100mg/ml	40	60mg / 0.6ml	60 od	0.60
Solution for Injection Clexane (Enoxaparin Sodium) syringes	45 50	80mg / 0.8ml	67.5 od 75 od	0.675 0.75
	55	100mg / 1ml	82.5 od	0.825
	60	100mg / 1ml	90 od	0.90
	65	100mg / 1ml	97.5 od	0.975
150mg/ml	70	120mg /	105 od	0.70
Solution for Injection	75	120mg /	112.5 od	0.76
(Enoxaparin Sodium) Forte	80	120mg /	120 od	0.80
syringes	85	150mg / 1ml	127.5 od	0.86
	90	150mg / 1ml	135 od	0.90
	95	150mg / 1ml	142.5 od	0.96
	100	150mg / 1ml	150 od	1.00

Please be aware that in some cases it is not possible to achieve an exact dose due to the graduations on the syringe and so some of the volumes recommended in this table have been rounded up to the nearest graduation.

Treatment of unstable angina and non-Q-wave myocardial infarction:

The recommended dose is 1 mg/kg Enoxaparin Sodium every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 325mg once daily).

Treatment with Enoxaparin Sodium in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilisation. The usual duration of treatment is 2 to 8 days.

Dosage chart for 1mg/kg SC treatment of UA or NSTEMI				
Patient weight	**Kg**	**Syringe label**	**Dose (mg)**	**Injection volume**
100mg/ml	40	40mg /	40 bd	0.40
Solution for Injection Clexane (Enoxaparin	45 50	60mg / 0.6ml	45 bd 50 bd	0.45 0.50
	55	60mg /	55 bd	0.55
	60	60mg /	60 bd	0.60
	65	80mg /	65 bd	0.65
	70	80mg /	70 bd	0.70
	75	80mg /	75 bd	0.75
	80	80mg /	80 bd	0.80
	85	100mg / 1ml	85 bd	0.85
	90	100mg / 1ml	90 bd	0.90
	95	100mg / 1ml	95 bd	0.95
	100	100mg / 1ml	100 bd	1.00
150mg/ml	105	120mg /	105 bd	0.70
Solution for Injection	110	120mg /	110 bd	0.74
(Enoxaparin Sodium) Forte	115	120mg /	115 bd	0.78
syringes	120	120mg /	120 bd	0.80
	125	150mg / 1ml	125 bd	0.84
	130	150mg / 1ml	130 bd	0.88
	135	150mg / 1ml	135 bd	0.90
	140	150mg / 1ml	140 bd	0.94
	145	150mg / 1ml	145 bd	0.98
	150	150mg / 1ml	150 bd	1.00

Please be aware that in some cases it is not possible to achieve an exact dose due to the graduations on the syringe and so some of the volumes recommended in this table have been rounded up to the nearest graduation.

Treatment of acute ST-segment Elevation Myocardial Infarction:

The recommended dose of enoxaparin sodium is a single IV bolus of 30mg plus a 1mg/kg SC dose followed by 1mg/kg administered SC every 12 hours (max 100mg for the first two doses only, followed by 1mg/kg dosing for the remaining doses). For dosage in patients ≥75

years of age, see section 4.2 Posology and method of administration: *Elderly*.

Dosage chart for 1mg/kg SC treatment of STEMI				
Patient weight	**Kg**	**Syringe label**	**Dose (mg)**	**Injection volume (ml)**
100mg/ml	40	40mg / 0.4ml	40 bd	0.40
Solution for Injection Clexane (Enoxaparin	45 50 55	60mg / 0.6ml 60mg /	45 bd 50 bd 55 bd	0.45 0.50 0.55
	60	60mg / 0.6ml	60 bd	0.60
	65	80mg / 0.8ml	65 bd	0.65
	70	80mg / 0.8ml	70 bd	0.70
	75	80mg / 0.8ml	75 bd	0.75
	80	80mg / 0.8ml	80 bd	0.80
	85	100mg / 1ml	85 bd	0.85
	90	100mg / 1ml	90 bd	0.90
	95	100mg / 1ml	95 bd	0.95
	100	100mg / 1ml	100 bd	1.00
150mg/ml	105	120mg / 0.8ml	105 bd **(1)**	0.70 **(1)**
Solution for Injection	110	120mg / 0.8ml	110 bd **(1)**	0.74 **(1)**
Clexane (Enoxaparin	115	120mg / 0.8ml	115 bd **(1)**	0.78 **(1)**
Sodium) Forte	120	120mg / 0.8ml	120 bd **(1)**	0.80 **(1)**
	125	150mg / 1ml **(1)**	125 bd **(1)**	0.84 **(1)**
	130	150mg / 1ml **(1)**	130 bd **(1)**	0.88 **(1)**
	135	150mg / 1ml **(1)**	135 bd **(1)**	0.90 **(1)**
	140	150mg / 1ml **(1)**	140 bd **(1)**	0.94 **(1)**
	145	150mg / 1ml **(1)**	145 bd **(1)**	0.98 **(1)**
	150	150mg / 1ml **(1)**	150 bd **(1)**	1.00 **(1)**

(1) Not to be given for the first two doses - (maximum 100mg for the first two doses only, followed by 1mg/kg dosing for the remaining doses)

Please be aware that in some cases it is not possible to achieve an exact dose due to the graduations on the syringe and so some of the volumes recommended in this table have been rounded up to the nearest graduation.

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. All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and maintained under (75 to 325mg once daily) unless contraindicated.

The recommended duration of enoxaparin sodium treatment is 8 days or until hospital discharge, whichever comes first.

For patients managed with Percutaneous Coronary Intervention (PCI): If the last enoxaparin sodium SC administration 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 0.3mg/kg of enoxaparin sodium should be administered.

Prevention of extracorporeal thrombus formation during haemodialysis:

A dose equivalent to 1 mg/kg (100 IU/kg) introduced into the arterial line at the beginning of a dialysis session is usually sufficient for a 4 hour session. If fibrin rings are found, such as after a longer than normal session, a further dose of 0.5 to 1mg/kg (50 to 100 IU/kg) may be given. For patients at a high risk of haemorrhage the dose should be reduced to 0.5 mg/kg (50 IU/kg) for double vascular access or 0.75 mg/kg (75 IU/kg) for single vascular access.

Elderly:

For treatment of acute ST-segment Elevation Myocardial Infarction in elderly patients ≥75 years of age, do not use an initial IV bolus. Initiate dosing with 0.75mg/kg SC every 12 hours (maximum 75mg for the first two doses only, followed by 0.75mg/kg dosing for the remaining doses).

For other indications, no dosage adjustments are necessary in the elderly, unless kidney function is impaired (see also section 4.2 Posology and method of administration: *Renal impairment*; section 4.4 Special warnings and precautions for use: *Haemorrhage in the elderly*; *Renal impairment, and Monitoring*; section 5.2 Pharmacokinetic properties).

Dosage chart for 0.75mg/kg SC treatment of STEMI (elderly patients aged ≥75 years only)					
Patient weight	**Kg**	**Syringe label**	**0.75mg/ kg Dose (mg)**	**Adjusted dosing (mg)**	**Injection volume (ml)**
100mg/ml Solution for Injection Clexane (Enoxaparin Sodium) syringes	40 45 50 55 60 65 70 75 80	60mg / 0.6ml 60mg / 0.6ml 60mg / 0.6ml 60mg / 0.6ml 60mg / 0.6ml 60mg / 0.6ml	30 bd 33.75 bd 37.5 bd 41.25 bd 45 bd 48.75 bd 52.5 bd 56.25 bd 60 bd	30 bd 35 bd 37.5 bd 42.5 bd 45 bd 50 bd 52.5 bd 57.5 bd 60 bd	0.30 0.35 0.375 0.425 0.45 0.5 0.525 0.575 0.60

		60mg / 0.6ml 60mg / 0.6ml 60mg / 0.6ml			
	85 90 95 100 105	80mg / 0.8ml 80mg / 0.8ml 80mg / 0.8ml 80mg / 0.8ml 80mg / 0.8ml	63.75 bd 67.5 bd 71.25 bd 75 bd 78.75 bd **(1)**	65 bd 67.5 bd 72.5 bd 75 bd 80 bd **(1)**	0.65 0.675 0.725 0.75 0.80 **(1)**
	110 115 120 125 130	100mg / 1ml 100mg / 1ml 100mg / 1ml 100mg / 1ml 100mg / 1ml	82.5 bd **(1)** 86.25 bd **(1)** 90 bd **(1)** 93.75 bd **(1)** 97.5 bd **(1)**	82.5 bd **(1)** 87.5 bd **(1)** 90 bd **(1)** 95 bd **(1)** 97.5 bd **(1)**	0.825 **(1)** 0.875 **(1)** 0.90 **(1)** 0.95 **(1)** 0.975 **(1)**
150mg/ml Solution for Injection Clexane (Enoxaparin Sodium) Forte syringes	135 140 145 150	120mg / 0.8ml 120mg / 0.8ml 120mg / 0.8ml 120mg / 0.8ml	101.25 bd **(1)** 105 bd **(1)** 108.75 bd **(1)** 112.5 bd **(1)**	102 bd **(1)** 105 bd **(1)** 111 bd **(1)** 114 bd **(1)**	0.68 **(1)** 0.7 **(1)** 0.74 **(1)** 0.76 **(1)**

(1) not to be given for the first two doses - (maximum 75mg for the first two doses only, followed by 0.75mg/kg dosing for the remaining doses)

Please be aware that in some cases it is not possible to achieve an exact dose due to the graduations on the syringe and so some of the volumes recommended in this table have been rounded up to the nearest graduation.

Children: Not recommended, as dosage not established.

Renal impairment: (See also section 4.4 Special warnings and precautions for use: *Renal impairment and Monitoring*; section 5.2 Pharmacokinetic properties).

Severe renal impairment:

A dosage adjustment is required for patients with severe renal impairment (creatinine clearance < 30 ml/min), according to the following tables, since enoxaparin sodium exposure is significantly increased in this patient population:

Dosage adjustments for therapeutic dosage ranges

Standard dosing	**Severe renal impairment**
1 mg/kg SC twice daily	1 mg/kg SC once daily
1.5 mg/kg SC once daily	1 mg/kg SC once daily
For treatment of acute STEMI in patients <75 years of age	
30mg-single IV bolus plus a 1mg/kg SC dose followed by 1mg/kg twice daily. (Max 100mg for each of the first two SC doses)	30mg-single IV bolus plus a 1mg/kg SC dose followed by 1mg/kg once daily. (Max 100mg for first SC dose only)
For treatment of acute STEMI in elderly patients ≥75 years of age	
0.75mg/kg SC twice daily without initial bolus. (Max 75mg for each of the first two SC doses)	1mg/kg SC once daily without initial bolus. (Max 100mg for first SC dose only)

Dosage adjustments for prophylactic dosage ranges

Standard dosing	**Severe renal impairment**
40 mg SC once daily	20 mg SC once daily
20 mg SC once daily	20 mg SC once daily

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

Moderate and mild renal impairment:

Although no dosage adjustments are recommended in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) or mild renal impairment (creatinine clearance 50-80 ml/min), careful clinical monitoring is advised.

Hepatic impairment: In the absence of clinical studies, caution should be exercised.

Body weight:

No dosage adjustments are recommended in obesity or low body weight (see also section 4.4 Special warnings and precautions for use: *Low body weight and Monitoring*; section 5.2 Pharmacokinetic properties).

Enoxaparin Sodium is administered by subcutaneous injection for the prevention of venous thromboembolic disease, treatment of deep vein thrombosis or for the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST elevation myocardial infarction (STEMI); through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extra-corporeal circulation during haemodialysis; and via intravenous (bolus) injection through an intravenous line only for the initial dose of acute STEMI indication and before PCI when needed. It must not be administered by the intramuscular route.

To avoid accidental needle stick after injection, the prefilled syringes are fitted with an automatic safety device

Subcutaneous injection technique

The prefilled disposable syringe is ready for immediate use. Enoxaparin Sodium should be administered when the patient is lying down by deep subcutaneous 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 held between the thumb and index finger. The skin fold should not be released until the injection is complete.

Once the plunger is fully pressed down the safety device is activated automatically. This protects the used needle.

Note: The plunger has to be pressed down all the way for the safety device to be activated. Do not rub the injection site after administration.

Intravenous (Bolus) Injection Technique (for acute STEMI indication only):

For intravenous injection, either the Multidose Vial or 60mg, 80mg or 100mg prefilled syringes can be used. Enoxaparin sodium should be administered through an intravenous line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of enoxaparin sodium with all other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous 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 30mg bolus**

For the initial 30mg bolus, using an enoxaparin sodium graduated prefilled syringe (60, 80 or 100mg), expel the excessive volume to retain only 30mg (0.3ml) in the syringe. The 30mg 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 insertion**

For patients being managed with Percutaneous Coronary Intervention (PCI), an additional IV bolus of 0.3mg/kg is to be administered if last SC administration was given more than 8 hours before balloon inflation (see section 4.2 Posology and method of administration: *Treatment of acute ST-segment Elevation Myocardial Infarction*).

In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug to 3mg/ml.

To obtain a 3mg/ml solution, using a 60mg enoxaparin sodium prefilled syringe, it is recommended to use a 50ml infusion bag (i.e. using either normal saline solution (0.9%) or 5% dextrose in water) as follows:

Withdraw 30ml from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 60mg enoxaparin sodium prefilled syringe into the 20ml remaining in the bag. Gently mix the contents of the bag. Withdraw the required volume of diluted solution with a syringe for administration into the intravenous line (using an appropriate injection site or port).

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 and to discard any remaining solution immediately after use.

Volume to be injected through intravenous line after dilution is completed

Weight	Required dose (0.3 mg/kg)	Volume to inject when diluted to a final concentration of 3 mg/ml
[Kg]	[mg]	[ml]
45	13.5	4.5
50	15	5
55	16.5	5.5

60	18	6
65	19.5	6.5
70	21	7
75	22.5	7.5
80	24	8
85	25.5	8.5
90	27	9
95	28.5	9.5
100	30	10
105	31.5	10.5
110	33	11
115	34.5	11.5
120	36	12
125	37.5	12.5
130	39	13
135	40.5	13.5
140	42	14
145	43.5	14.5
150	45	15

4.3 Contraindications

Contraindicated in patients with acute bacterial endocarditis, active major bleeding and conditions with a high risk of uncontrolled haemorrhage, including recent haemorrhagic stroke, thrombocytopenia in patients with a positive in-vitro aggregation test in the presence of enoxaparin; active gastric or duodenal ulceration; hypersensitivity to either enoxaparin sodium, heparin or its derivatives including other Low Molecular Weight Heparins; in patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedures is contraindicated.

4.4 Special warnings and precautions for use

Low Molecular Weight Heparins should not be used interchangeably since they differ in their manufacturing process, molecular weights, specific anti Xa activities, units and dosage. This results in differences in pharmacokinetics and associated biological activities (e.g. anti-IIa

activity, and platelet interactions). Special attention and compliance with the instructions for use specific to each proprietary medicinal product are therefore required.
Enoxaparin is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia with or without thrombosis.

As there is a risk of antibody-mediated heparin-induced thrombocytopenia also occurring with low molecular weight heparins, regular platelet count monitoring should be considered prior to and during therapy with these agents. Thrombocytopenia, should it occur, usually appears between the 5th and the 21st day following the beginning of therapy. 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. 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 therapy.

Enoxaparin injection, 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, uncontrolled severe arterial hypertension, diabetic retinopathy, recent neuro- or ophthalmologic surgery.

As with other anticoagulants, bleeding may occur at any site (see section 4.8 Undesirable effects). If bleeding occurs, and sometimes anaemia, the origin of the haemorrhage should be investigated and appropriate treatment instituted.

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

As with other anti-coagulants, there have been cases of intra-spinal haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal punctureresulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 40 mg od or lower. The risk is greater with higher enoxaparin sodium dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional drugs affecting haemostasis such as NSAIDs (see section 4.5 Interaction with

other medicinal products and other forms of interaction). The risk also appears to be increased by traumatic or repeated neuraxial 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 anaesthesia/analgesia, the pharmacokinetic profile of the drug should be considered (see section 5.2 Pharmacokinetic properties). Placement and removal of the catheter is best performed when the anticoagulation effect of enoxaparin is low.

Placement or removal of a catheter should be delayed for 10 - 12 hours after administration of DVT prophylactic doses of enoxaparin sodium, whereas patients receiving higher doses of enoxaparin sodium (1.5 mg/kg once daily) will require longer delays (24 hours). The subsequent enoxaparin sodium dose should be given no sooner than 4 hours after catheter removal.

Should the physician decide to administer anticoagulation in the context of epidural/spinal anaesthesia, extreme vigilance and 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. Patients should be instructed to inform their nurse or physician immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

Percutaneous coronary revascularisation procedures:

To minimise the risk of bleeding following vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-elevation myocardial infarction, adhere precisely to the intervals recommended between enoxaparin sodium 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, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If treatment 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.

For some patients with pulmonary embolism (e.g. those with severe haemodynamic instability) alternative treatment such as thrombolysis or surgery may be indicated.

Prosthetic Heart Valves

There have been no adequate studies to assess the safe and effective use of enoxaparin sodium in preventing valve thrombosis in patients with prosthetic heart valves. Prophylactic doses of enoxaparin are not sufficient to prevent valve thrombosis in patients with prosthetic heart valves. Confounding factors, including underlying diseases and insufficient clinical data, limit the evaluation of these cases. Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant doses (see section 4.6 Pregnancy and lactation). The use of enoxaparin sodium cannot be recommended for this purpose.

Haemorrhage in the elderly: No increased bleeding tendency is observed in the elderly within the prophylactic dosage ranges. Elderly patients (especially patients aged eighty years and above) may be at an increased risk for bleeding complications within the therapeutic dosage ranges. In the treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), an increase in bleeding events was observed in patients aged 65-75 years suggesting these patients might be at particular risk of bleeding. Careful clinical monitoring is advised (see also section 4.2 Posology and method of administration: Elderly; section 5.2 Pharmacokinetic properties).

Renal impairment: In patients with renal impairment, there is an increase in enoxaparin exposure which increases the risk of bleeding. Since enoxaparin exposure is significantly increased in patients with severe renal impairment (creatinine clearance < 30 ml/min) dosage adjustments are recommended in therapeutic and prophylactic dosage ranges. Although no dosage adjustments are 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 (see also section 4.2 Posology and method of administration: Renal impairment; section 5.2 Pharmacokinetic properties).In the treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), the data are limited in patients with creatinine levels above 220 and 175 µmol/L for males and females respectively.

Low body weight: In low-weight women (< 45 kg) and low-weight men (< 57 kg), an increase in enoxaparin exposure has been observed within the prophylactic dosage ranges (non-weight adjusted), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients (see also section 5.2 Pharmacokinetic properties).

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.

Monitoring: Risk assessment and clinical monitoring are the best predictors of the risk of potential bleeding. Routine anti-Xa activity monitoring is usually not required. However, anti-Xa activity monitoring might be considered in those patients treated with LMWH who also have either an increased risk of bleeding (such as those with renal impairment, elderly and extremes of weight) or are actively bleeding.

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 APTT (activated partial thromboplastin time) and ACT (activated clotting time) 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.

4.5 Interaction with other medicinal products and other forms of interaction

It is recommended that agents which affect haemostasis should be discontinued prior to enoxaparin therapy unless their use is essential, such as: systemic salicylates, acetylsalicylic acid, NSAIDs including ketorolac, dextran, and clopidogrel, systemic glucocorticoids, thrombolytics and anticoagulants. If the combination cannot be avoided, enoxaparin should be used with careful clinical and laboratory monitoring.

4.6 Pregnancy and lactation

Pregnancy: Animal studies have not shown any evidence of foetotoxicity or teratogenicity. In the pregnant rat, the transfer of 35S-enoxaparin across the maternal placenta to the foetus is minimal.

In humans, there is no evidence that enoxaparin crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the first and the third trimesters.

As there are no adequately powered and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need.

Pregnant women with mechanical prosthetic heart valves

The use of enoxaparin 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 (1 mg/kg bid) 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 postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism. Enoxaparin sodium is not recommended for use in pregnant women with prosthetic heart valves (see section 4.4 Special warnings and precautions for use: Prosthetic heart valves).

Lactation: In lactating rats, the concentration of ^{35}S-enoxaparin or its labelled metabolites in milk is very low.

It is not known whether unchanged enoxaparin is excreted in human breast milk. The oral absorption of enoxaparin is unlikely. However, as a precaution, lactating mothers receiving enoxaparin should be advised to avoid breast-feeding

4.7 Effects on ability to drive and use machines

Enoxaparin has no effect on the ability to drive and operate machines

4.8 Undesirable effects

The adverse reactions observed in clinical studies and reported in 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 available data). Post-marketing adverse reactions are designated with a frequency “not known”.

Haemorrhages

In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients[1]). Some of these cases have been fatal.

As with other anticoagulants, haemorrhage may occur during enoxaparin therapy 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 section 4.5). The origin of the bleeding should be investigated and appropriate treatment instituted.

MedDRA 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
Vascular disorders	*Very common*: Haemorrhage *	*Common:* Haemorrhage	*Very common:* Haemorrhage *	*Common:* Haemorrhage *	*Common:* Haemorrhage *
	Rare: Retroperitoneal haemorrhage	*	*Uncommon:* Intracranial haemorrhage, Retroperitoneal haemorrhage	*Rare:* Retroperitoneal haemorrhage	*Uncommon:* Intracranial haemorrhage, Retroperitoneal haemorrhage

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

[1] In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by an haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.

Thrombocytopenia and thrombocytosis

MedDRA 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* *Common*: Thrombo-cytopenia	*Uncommon*: Thrombo-cytopenia	*Very common*: Thrombocytosis* Common: Thrombo-cytopenia	*Uncommon*: Thrombo-cytopenia	*Common*: Thrombocytosis* Thrombo-cytopenia *Very rare*: Immuno-allergic thrombo-cytopenia

*: Platelet increased > 400 G/L

Other clinically relevant adverse reactions

These reactions are presented below, whatever the indications, by system organ class, frequency grouping and decreasing order of seriousness.

MedDRA system organ class	All indications
Immune system disorders	*Common:* Allergic reaction *Rare:* Anaphylactic / anaphylactoid reaction
Hepatobilary disorders	*Very common:* Hepatic enzymes increase (mainly transaminases **)
Skin and subcutaneous tissue disorders	*Common:* Urticaria, pruritus, erythema, *Uncommon:* Bullous dermatitis
General disorders and administration site conditions	*Common:* Injection site haematoma, injection site pain, other injection site reaction* *Uncommon:* Local irritation; skin necrosis at injection site
Investigations	*Rare:* Hyperkaliemia

*: such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction (NOS)

**: transaminases levels > 3 times the upper limit of normality

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 Regulatory Authority.

4.9 Overdose

Orally administered enoxaparin is poorly absorbed and even large oral doses should not lead to any serious consequences. This may be checked by plasma assays of anti-Xa and anti-IIa activities.

Accidental overdose following parenteral administration may produce haemorrhagic complications. The anticoagulant effects can be largely neutralised by the slow intravenous injection of Protamine, but even with high doses of Protamine, the anti-Xa activity of enoxaparin sodium is never completely neutralised (maximum about 60%). The initial dose of Protamine depends on the dose of enoxaparin given and also consideration of the maximum recommended Protamine dose (50mg). Data on Protamine dosing in humans for enoxaparin overdose is extremely limited. The available data suggest that in the first 8 hours after enoxaparin administration 1mg Protamine should neutralise the effects of 1mg of enoxaparin. Where the dose of enoxaparin has exceeded 50mg, an initial dose of 50mg Protamine would be appropriate, based on the maximum recommended single protamine dose. Decisions regarding the necessity and dose of subsequent Protamine injections should be based on clinical response rather than measurement of anti Xa or anti XIIa results. The physician should also consider that the amount of enoxaparin in the body drops to 50% after 8 hours and 33% or less after 12 hours. The dose of Protamine should be adjusted depending on the length of time since enoxaparin was administered

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent, heparin group. ATC code B01A B05

Enoxaparin is a low molecular weight heparin with a mean molecular weight of approximately 4,500 daltons. The drug substance is the sodium salt. The molecular weight distribution is:

<2000 daltons ≤20%
2000 to 8000 daltons ≥68%
>8000 daltons ≤18%

Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4- enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin

structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain. Enoxaparin sodium is characterised by a higher ratio of antithrombotic activity to anticoagulant activity than unfractionated heparin. At recommended doses, it does not significantly influence platelet aggregation, binding of fibrinogen to platelets or global blood clotting tests such as APTT and prothrombin time.

Enoxaparin binds to anti-thrombin III leading to inhibition of coagulation factors IIa and Xa. Enoxaparin has been shown to increase the blood concentration of Tissue Factor Pathway Inhibitor in healthy volunteers.

5.2 Pharmacokinetic properties

Enoxaparin is rapidly and completely absorbed following subcutaneous injection. The maximum plasma anti-Xa activity occurs 1 to 4 hours after injection with peak activities in the order of 0.16 IU/ml and 0.38 IU/ml after doses of 20 mg or 40 mg respectively. The anti-Xa activity generated is localised within the vascular compartments and elimination is characterised by a half life of 4 to 5 hours. Following a 40 mg dose, anti-Xa activity may persist in the plasma for 24 hours.
A 30mg IV bolus immediately followed by a 1mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1.16IU/ml (n=16) and average exposure corresponding to 88% of steady state levels.
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. In patients with severe renal impairment (creatinine clearance < 30 ml/min), the AUC at steady state is significantly increased by an average of 65% after repeated, once daily subcutaneous doses of 40mg.
Hepatic metabolism by desulphation and depolymerisation also contributes to elimination. The elimination half life may be prolonged in elderly patients although no dosage adjustment is necessary.
A study of repeated, once daily subcutaneous doses of 1.5 mg/kg in healthy volunteers suggests that no dosage adjustment is necessary in obese subjects (BMI 30-48 kg/m2) compared to non-obese subjects.

Enoxaparin, as detected by anti-Xa activity, does not cross the placental barrier during the second trimester of pregnancy.

Low Body Weight
When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 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 Special warnings and precautions for use: Low Body Weight).

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

5.3 Preclinical safety data

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin.

Enoxaparin was not mutagenic in in vitro tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the in vivo rat bone marrow chromosomal aberration test.

Enoxaparin 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. Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin.

Besides the anticoagulant effects of enoxaparin, there was no evidence of adverse effects at 15 mg/kg/day in the 13-week subcutaneous toxicity studies both in rats and dogs and at 10 mg/kg/day in the 26-week subcutaneous and intravenous toxicity studies both in rats and monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl Alcohol
Water for Injection

6.2 Incompatibilities

Subcutaneous Injection
Enoxaparin Sodium should not be mixed with any other injections or infusions.

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool and dry place, protect from light and moisture. Do not store above 25°C. Do not store in a refrigerator or freezer. Keep out of the reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each box contains 1 pre-filled syringe containing Enoxaparin Sodium BP in blister pack
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder

SQUARE Pharmaceuticals Ltd.
48 Mohakhali Commercial Area,
Dhaka - 1212.
Bangladesh

8. Marketing Authorisation Number

H2022/CTD8805/18577

9. Date of First Authorisation / Renewal of Authorisation

2022 September 21

10. Date of Revision of The Text

2022 September 21