AUSTRALIAN PRODUCT INFORMATION – CLEXANE AND CLEXANE FORTE (ENOXAPARIN SODIUM)

1 NAME OF THE MEDICINE

Enoxaparin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clexane

Ready-to-use, prefilled syringes:

20 mg injection: enoxaparin sodium 20 mg/0.2 mL (anti-Xa: 2,000 IU)

40 mg injection: enoxaparin sodium 40 mg/0.4 mL (anti-Xa: 4,000 IU)

Ready-to-use, prefilled syringes with graduated markings:

60 mg injection: enoxaparin sodium 60 mg/0.6 mL (anti-Xa: 6,000 IU)

80 mg injection: enoxaparin sodium 80 mg/0.8 mL (anti-Xa: 8,000 IU)

100 mg injection: enoxaparin sodium 100 mg/1 mL (anti-Xa: 10,000 IU)

Clexane (with safety lock system)

Ready-to-use, prefilled syringes:

20 mg injection: enoxaparin sodium 20 mg/0.2 mL (anti-Xa: 2,000 IU)

40 mg injection: enoxaparin sodium 40 mg/0.4 mL (anti-Xa: 4,000 IU)

Ready-to-use, prefilled syringes with graduated markings

60 mg injection: enoxaparin sodium 60 mg/0.6 mL (anti-Xa: 6,000 IU)

80 mg injection: enoxaparin sodium 80 mg/0.8 mL (anti-Xa: 8,000 IU)

100 mg injection: enoxaparin sodium 100 mg/1 mL (anti-Xa: 10,000 IU)

Clexane (with Eris safety lock system)

Ready-to-use, prefilled syringes:

20 mg injection: enoxaparin sodium 20 mg/0.2 mL (anti-Xa: 2,000 IU)

40 mg injection: enoxaparin sodium 40 mg/0.4 mL (anti-Xa: 4,000 IU)

Ready-to-use, prefilled syringes with graduated markings

60 mg injection: enoxaparin sodium 60 mg/0.6 mL (anti-Xa: 6,000 IU)

80 mg injection: enoxaparin sodium 80 mg/0.8 mL (anti-Xa: 8,000 IU)

100 mg injection: enoxaparin sodium 100 mg/1 mL (anti-Xa: 10,000 IU)

Clexane Forte

Ready-to-use, prefilled syringes with double graduated markings:

120 mg injection: 120 mg/0.8 mL (anti-Xa: 12,000 IU)

150 mg injection: 150 mg/1 mL (anti-Xa: 15,000 IU)

Clexane Forte (with safety lock system)

Ready-to-use, prefilled syringes with double graduated markings:

120 mg injection: 120 mg/0.8 mL (anti-Xa: 12,000 IU)

150 mg injection: 150 mg/1 mL (anti-Xa: 15,000 IU)

Clexane Forte (with Eris safety lock system)

Ready-to-use, prefilled syringes with double graduated markings:

120 mg injection: 120 mg/0.8 mL (anti-Xa: 12,000 IU)

150 mg injection: 150 mg/1 mL (anti-Xa: 15,000 IU)

For the full list of excipients, see Section 6.1 List of excipients

3 PHARMACEUTICAL FORM

Injection, solution

Clear, colourless to pale yellow solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Prevention of thrombo-embolic disorders of venous origin in patients undergoing orthopaedic and general surgery.
- Prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness.
- Prevention of thrombosis in extra-corporeal circulation during haemodialysis.

- Treatment of established deep vein thrombosis.

- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.

- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) as an adjunctive to thrombolytic treatment, including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

4.2 DOSE AND METHOD OF ADMINISTRATION

For subcutaneous use: do not mix CLEXANE with other injections or solutions.

For intravenous use: see Treatment of Acute ST-segment Elevation Myocardial Infarction.

Prophylaxis of Venous Thrombosis

Prophylaxis against thromboembolism should be tailored according to the patient's risk. Risk factors include age over 40 years, history of deep vein thrombosis or pulmonary embolism, surgery and other trauma, prolonged immobilisation, cardiac disease, obesity, malignancy, varicose veins, hypercoagulable states, pregnancy and the puerperium, oral contraceptives, severe infection, inflammatory bowel disease.

a) High Risk Patients

In patients with high risk of thromboembolism, a CLEXANE dosage of 40 mg (0.4 mL; anti-Xa: 4000 IU) should be administered subcutaneously once daily. In high risk patients undergoing surgery, the initial dose should be given approximately 12 hours preoperatively. The timing of the first dose may need to be modified if spinal/epidural anaesthesia is to be performed (see Section 4.4 – Special warnings and precautions for use: Spinal/Epidural Anaesthesia).

b) Moderate Risk Patients

In patients with a moderate risk of thromboembolism, the recommended CLEXANE dosage is 20 mg (0.2 mL; anti-Xa: 2000 IU) subcutaneously once daily. In moderate risk patients undergoing surgery, the initial dose should be given approximately 2 hours preoperatively. The timing of the first dose may need to be modified if spinal/epidural anaesthesia is to be performed (see Section 4.4 - Special warnings and precautions for use: Spinal/Epidural Anaesthesia).

Duration of Therapy

High to Moderate Risk: Prophylaxis should be continued for 7 to 10 days or until the risk of thromboembolism has diminished.

Prolonged Thromboprophylaxis

Therapy with 40 mg once daily for 30 post-operative days has been proven to be beneficial in total hip replacement surgery.

Under normal conditions of use, CLEXANE does not modify global clotting tests and therefore there is no need to perform these tests in order to monitor therapy.

Prophylaxis of Venous Thromboembolism in Medical Patients

The recommended dose should be 40 mg once daily by subcutaneous injection for a minimum of 6 days, continuing for a maximum of 14 days or less if the patient returns to full ambulation earlier than 14 days.

Treatment of Deep Venous Thrombosis

The initial clinical trials which established the efficacy of CLEXANE in the treatment of deep venous thrombosis were conducted on patients who were initially treated with heparin and then changed to CLEXANE when a definitive diagnosis was established. However, the use of heparin prior to CLEXANE is not currently recommended. The average duration of therapy in the clinical trials was 10 days. No data are available on the safety of long term treatment. Data on use in patients over 65 years of age in these trials were limited.

The recommended dosage for treatment of established deep vein thrombosis with CLEXANE is 1.5 mg/kg body weight once daily (150 IU anti-Xa activity/kg bodyweight) or 1 mg/kg body weight (100 IU anti-Xa activity/kg bodyweight) twice daily subcutaneously. In high risk patients, e.g. the obese or patients with baseline iliac vein thrombosis or cancer, a dose of 1 mg/kg body weight administered twice daily may be more beneficial.

Warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of commencing CLEXANE initiation). CLEXANE should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0).

Treatment of Unstable Angina and Non-Q-Wave-Myocardial Infarction

The recommended dose of CLEXANE is 1 mg/kg (100 IU anti-Xa activity/kg) every 12 hours by subcutaneous injection, administered concurrently with oral aspirin.

Treatment with CLEXANE in these patients should be prescribed for a minimum of 2 days and a maximum of 8 days.

Treatment of Acute ST-segment Elevation Myocardial Infarction

In patients with acute ST-segment elevation myocardial infarction, administered in conjunction with a fibrinolytic (fibrin-specific or non-fibrin specific), the recommended dose of CLEXANE is a single IV bolus of 30 mg plus a 1 mg/kg SC dose, followed by 1 mg/kg administered SC every 12 hours (maximum 100 mg for each of the first two SC doses only, followed by 1 mg/kg dosing for the remaining doses). For dosage in patients ≥75 years of age, see Section 4.2 - Dose and method of administration: Use in Renal Impairment and Use in the Elderly.

When administered in conjunction with a thrombolytic (fibrin-specific or non-fibrin specific), CLEXANE should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. All patients should receive aspirin as soon as they are identified as having STEMI (100 to 300 mg once daily, unless contraindicated). The recommended duration of CLEXANE treatment is 8 days or until hospital discharge, whichever comes first.

For patients further managed with Percutaneous Coronary Intervention (PCI): If the last CLEXANE SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last CLEXANE SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of CLEXANE should be administered (see Section 4.4 - Special warnings and precautions for use: Percutaneous Coronary Revascularisation Procedures).

Haemodialysis

In patients undergoing repeated sessions of haemodialysis, the prevention of thrombosis in the extracorporeal blood circuit is obtained by injection of a dose of 1 mg/kg (100 IU anti-Xa activity/kg) into the arterial line of the dialysis circuit at the start of the session. This dose is usually sufficient for a 4-hour haemodialysis session. If fibrin rings are formed, a fresh injection of 0.5 to 1 mg/kg (50 to 100 IU anti-Xa activity/kg) should be made depending on the time before the end of the dialysis.

In haemodialysed patients with a high risk of haemorrhage, (in particular, in pre or post-operative dialysed patients) or with a progressive haemorrhagic disorder, the dialysis sessions may be carried out by using a dose of 0.5 mg/kg (50 IU anti-Xa activity/kg) (double vascular access) or 0.75 mg/kg (75 IU anti-Xa activity/kg) (single vascular access).

Renal Impairment

A dosage adjustment is required for patients with severe renal impairment (creatinine clearance <30 mL/min) according to the following tables.

The following dosage adjustments are recommended for the prophylactic dosage ranges.

Table 1

Normal 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 following dosage adjustments are recommended for the treatment dosage ranges.

Table 2

Normal 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
Acute STEMI patients < 75 years of age	
30 mg-single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC twice daily (Max 100mg for each of the first two SC doses)	30 mg-single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC once daily (Max 100mg for first SC dose only)
Acute STEMI patients ≥ 75 years of age	
0.75 mg/kg SC twice daily without initial bolus (Max 75mg for each of the first two SC doses)	1 mg/kg SC once daily without initial bolus (Max 75mg for first SC dose only)

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 observation is advised for signs and symptoms of bleeding.

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 0.75 mg/kg SC every 12 hours (maximum 75 mg for each of the first two SC doses only, followed by 0.75 mg/kg dosing for the remaining doses; see Section 5.1 – Pharmacodynamic properties: Clinical trials). No dose reduction is necessary in the elderly for other indications, unless renal function is impaired, however careful clinical observation is advised (see Section 4.4 - Special warnings and precautions for use: Use in Renal Impairment and Use in the Elderly).

Children

The safety and efficacy of CLEXANE in children has not been established.

Hepatic Impairment

In the absence of clinical studies, caution should be used in hepatically impaired patients.

Subcutaneous Injection Technique

Injection should be made preferably when the patient is reclining. CLEXANE is administered by deep subcutaneous injection. Injection of CLEXANE should be alternated between the left and right anterolateral abdominal wall using a different site for each injection. Do not expel the air bubble from the syringe before the injection to avoid the loss of drug. CLEXANE contains no antimicrobial agent and should be used only once and then discarded.

The needles on prefilled syringes of CLEXANE are covered in a silicon coating, to enable ease of penetration. Do not wipe the needle or allow CLEXANE solution to crystallise on the needle prior to use, as this will damage the silicon coating. A “dart” injection technique should be used to administer CLEXANE. Do not rub the injection site after administration.

Intravenous (Bolus) Injection Technique (for the treatment of acute STEMI)

For intravenous injection, the graduated prefilled syringes should be used, see subsection below. CLEXANE should be administered through an intravenous line and should not be co-administered with other medications. To avoid the possible mixture of CLEXANE with 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 CLEXANE to clear the port of drug. CLEXANE may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

Prefilled Syringes

The prefilled syringes are ready for immediate use. The whole length of the needle should be introduced vertically (at a 90° angle to the skin) into the thickness of a skin fold gently held between the operator's thumb and finger. This skin fold should be held throughout the duration of the injection.

Graduated Prefilled Syringes

When using the 60 mg, 80 mg, 100 mg, 120 mg and 150 mg graduated prefilled syringes, the volume to be injected should be measured precisely according to the dosage recommended, without expelling the air bubble while adjusting dosage. If the dose required is exactly 60, 80, 100, 120 or 150 mg inject the full contents of the syringe. The whole length of the needle should be introduced vertically (at a 90° angle to the skin) into the thickness of a skin fold gently held between the operator's thumb and finger. This skin fold should be held throughout the duration of the injection.

4.3 CONTRAINDICATIONS

- Allergy to CLEXANE, heparin or its derivatives including other low molecular weight heparins.
- Acute bacterial endocarditis.
- Conditions with a high risk of uncontrolled haemorrhage including major bleeding disorders, focal lesions, haemorrhagic stroke, active ulcerative conditions showing a tendency to haemorrhage (e.g. peptic ulcer, ulcerative colitis).
- Thrombocytopenia associated with a positive *in vitro* test for anti platelet antibody in the presence of enoxaparin sodium.
- History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (see Section 4.4 Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

LOW MOLECULAR WEIGHT HEPARIN PRODUCTS ARE NOT CLINICALLY INTERCHANGEABLE.

They differ in their manufacturing process, molecular weights, specific anti-Xa activities, units and dosage. The biological activity of different low molecular weight heparins cannot be expressed in a test allowing for a simple dose comparison. Different low molecular weight heparins may not be bioequivalent in terms of their labelled anti-Xa activities and alternative products should not be introduced nor interchanged during a course of treatment.

Not to be administered by the intramuscular route.

Risk of Haemorrhage

CLEXANE should be used with extreme caution in conditions with increased risk of haemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors. Major haemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal. As with other anticoagulants, bleeding can occur at any site during therapy with CLEXANE (see Section 4.8 – Adverse effects (Undesirable effects)). If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instigated. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site and appropriate treatment instituted.

Concomitant Medical Conditions

CLEXANE should be used with caution in patients with the following conditions: hepatic insufficiency, a bleeding diathesis, uncontrolled arterial hypertension, a history of gastrointestinal ulceration, impaired haemostasis, recent ischaemic stroke, diabetic retinopathy, recent neuro- or ophthalmologic surgery and haemorrhage.

Heparin-Induced Thrombocytopenia

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 Contraindications). Circulating antibodies may persist for several years.

CLEXANE is to be used with extreme caution in patients with a history (more than 100 days) of heparin-induced (including low molecular weight heparins) thrombocytopenia without circulating antibodies. Circulating antibodies may persist for several years. If history of heparin-induced thrombocytopenia is suspected, *in vitro* platelet aggregation tests have limited predictive value. The decision to use CLEXANE in such a case must be made only after a careful benefit risk assessment and after non-heparin alternative treatments are considered, and only in consultation with an expert in the field.

Spinal/Epidural Anaesthesia

There have been rare cases of neuraxial haematomas reported with the concurrent use of CLEXANE and spinal/epidural anaesthesia resulting in long-term or permanent paralysis. These events are rare with CLEXANE dosage regimens 40 mg once daily or lower. The risk is greater with higher CLEXANE dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs) (see Section 4.5 - Interactions with other medicines and other forms of interactions). 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 CLEXANE and epidural or spinal anaesthesia/analgesia, the pharmacokinetic profile of the drug should be considered (see Section 5.2 – Pharmacokinetic properties). Placement and removal of the needle/catheter is best performed when the anticoagulant effect of enoxaparin is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Placement or removal of an epidural or spinal needle or catheter should be delayed for at least 12 hours after administration of lower doses (20mg once daily or 40mg once daily) of enoxaparin, and at least 24 hours after the administration of higher doses (0.75mg/kg twice

daily, 1 mg/kg twice daily, or 1.5mg/kg once daily) of enoxaparin. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial haematoma will be avoided. Patients receiving the 0.75mg/kg twice daily dose or the 1mg/kg twice daily dose should not receive the second enoxaparin dose in the twice daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent enoxaparin dose after catheter removal cannot be made, consider delaying this next dose for at least four hours, 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. For patients with creatinine clearance <30ml/minute, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin (20mg once daily or 40 mg once daily) and at least 48 hours for the higher dose (0.75mg/kg/twice daily, 1mg/kg/twice daily or 1.5mg/kg/once daily).The patient's regular CLEXANE dose may need to be delayed to ensure this. If blood is present during needle/catheter placement, the subsequent dose of CLEXANE should be delayed for 24 hours after placement.

Should the physician decide to administer anticoagulation in the context of epidural/spinal anaesthesia or lumbar puncture, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of spinal haematoma 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 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.

Thrombocytopenia

Thrombocytopenia can occur with the administration of CLEXANE. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in patients given CLEXANE, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given CLEXANE, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, CLEXANE should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

Prosthetic Heart Valves

There have been no adequate studies to assess the safe and effective use of CLEXANE in preventing thromboembolism in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and foetal death. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see Section 4.6 – Fertility, Pregnancy and Lactation). The use of CLEXANE cannot be recommended for this purpose.

Percutaneous Coronary Revascularisation Procedures

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

Use in Renal Impairment

In patients with renal impairment, there is an increase in exposure of CLEXANE which increases the risk of bleeding. Since exposure of CLEXANE is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. 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 observation is advised (see Section 4.2 – Dose and method of administration: Renal Impairment).

Pharmacokinetics of enoxaparin are altered in renal impairment. The extent to which a defect in platelet function in severe renal failure might further contribute to bleeding risk is unknown.

Use in Hepatic Impairment

See Section 4.2 Dose and method of administration

Low Weight

An increase in exposure of CLEXANE with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical observation is advised in these patients.

Obese Patients

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

Hyperkalaemia

Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia (see Section 4.8 – Adverse effects (Undesirable effects)), particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, taking medicinal products known to increase potassium (see Section 4.5 – Interactions with other medicines and other forms of interactions). Plasma potassium should be monitored regularly especially in patients at risk.

Use in the Elderly

No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially 80 years or older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical observation is advised. A

dosage adjustment may be necessary in elderly patients due to age-related impairment of renal function (see Section 4.2 – Dose and method of administration: Renal Impairment).

In the clinical study for treatment of acute STEMI, in patients ≥75 years of age (n = 2532) the rate of death or myocardial re-infarction was higher than in the global population but lower in the enoxaparin group (24.8%) than in the UFH group (26.3%, relative risk 0.94, p = 0.38). Patients ≥75 years of age did not receive a 30-mg IV bolus prior to the normal dosage regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours (see Section 4.2 - Dose and method of administration).

In patients ≥75 years of age, the rate of TIMI major bleeding was higher than in the global population and was higher in the enoxaparin group (3.3%) for patients ≥75 years of age compared with the UFH group (2.9%, RR 1.15, p=0.57).

Compared to younger patients (<65 years), the rate of TIMI major bleeding was higher in patients >65 years of age (respectively 1.2% and 2.5%) and was higher in the enoxaparin group as compared to the UFH group (see Section 5.1 – Pharmacodynamic properties: Clinical trials).

Paediatric Use

The safety and efficacy of enoxaparin sodium in children has not been established.

Effects on laboratory tests

At doses used for prophylaxis of venous thromboembolism, CLEXANE 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 and ACT (activated clotting time) may occur. Increases in aPTT and ACT are not linearly correlated with increasing CLEXANE antithrombotic activity and therefore are unsuitable and unreliable for monitoring CLEXANE activity.

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with CLEXANE. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of CLEXANE activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of CLEXANE in patients with significant renal impairment. If during CLEXANE therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of CLEXANE.

Monitoring of Platelet Count

The risk of antibody-mediated heparin-induced thrombocytopenia also exists with low molecular weight heparins. Should thrombocytopenia occur, it usually appears between the 5th and the 21st day following the beginning of CLEXANE treatment. Therefore, it is recommended that the platelet counts be measured before initiation of therapy with CLEXANE 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), CLEXANE treatment must be immediately discontinued and the patient switched to another therapy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clinical trials revealed no adverse effects that could be caused by drug interactions, including no pharmacokinetic interactions between enoxaparin and thrombolytics when administered concurrently.

It is recommended that agents which affect haemostasis should be discontinued prior to CLEXANE therapy unless strictly indicated. These agents include medications such as: anti-coagulants, thrombolytics, non-steroidal anti-inflammatory agents (including ketorolac), preparations containing aspirin, systemic salicylates, ticlopidine, Dextran 40, clopidogrel, other anti platelet agents including glycoprotein IIb/IIIa antagonists or systemic glucocorticoids. If the combination is indicated, CLEXANE should be used with careful clinical and laboratory monitoring of the haemostatic factors, when appropriate.

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 Section 4.4 - Special warnings and precautions for use and Section 4.8 – Adverse effects (Undesirable effects)).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy

Category C

In embryo-foetal development studies of enoxaparin there was no evidence of teratogenicity at 30 mg/kg/day SC or 160 mg/kg/day IV in either rats or rabbits. A reduction in rat pup weights occurred at 20 mg/kg/day enoxaparin SC only when administered during the late phase of gestation. An increase in post-implantation loss was noted at 160 mg/kg/day enoxaparin IV in rabbits, but not at 40 mg/kg/day IV, nor in rats at up to 160 mg/kg/day IV. Post-natal development in rats was not affected by doses tested up to a maximum of 20 mg/kg/day enoxaparin IV.

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

There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.

There have been post-marketing reports of foetal death when pregnant women received CLEXANE. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk of bleeding. Haemorrhage can occur at

any site and may lead to death of mother and/or foetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the foetus and the mother if enoxaparin is administered during pregnancy.

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 CLEXANE (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal death. There have been isolated post-marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism. In the absence of additional dosing, efficacy and safety information in this circumstance, CLEXANE is not recommended for use in pregnant women with mechanical prosthetic heart valves (Precautions: Prosthetic Heart Valves).

Use in lactation

It is unknown whether enoxaparin is excreted into the breast milk of humans. In lactating rats, the concentration of ^{35}S-enoxaparin sodium or its labelled metabolites in milk was similar to that in maternal plasma. Apart from lower birth weights and slightly delayed physical development, there were no significant adverse effects of 20 mg/kg/day enoxaparin SC in a peri- and post- natal study in rats. Effects of CLEXANE on lactating women have not been studied.

As a precaution, women should be advised not to breast feed while using CLEXANE.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Enoxaparin sodium has been evaluated in more than 15,000 patients. The following information relates to adverse events observed in controlled clinical trials with patients given CLEXANE prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications (n = 1176), prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility (n = 1169) , treatment of deep vein thrombosis with or without pulmonary embolism (n = 669) or with patients given CLEXANE for the treatment of unstable angina or non-Q-wave myocardial infarction, administered concurrently with aspirin (n = 1578) or with patients given CLEXANE for the treatment of acute ST-segment elevation myocardial infarction (n = 10176).

Reported adverse events are presented at frequencies of:

Very common ≥ 1/10 (10%)

common ≥ 1/100 (1%) and < 1/10 (10%)

uncommon ≥ 1/1000 (0.1%) and < 1/100 (1%)

rare ≥ 1/10000 (0.01%) and < 1/1000 (0.1%)

very rare < 1/10000 (<0.01%)

Haematological

Common: Anaemia

In clinical trials haemorrhages were the most commonly reported adverse effect. These included major haemorrhages, reported at most 4.2% in surgical patients receiving prophylaxis. Bleeding may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the use of medications affecting haemostasis (see Section 4.4 - Special warnings and precautions for use and Section 4.5 – Interactions with other medicines and other forms of interactions). Major haemorrhage, including retroperitoneal and intracranial bleeding, has been reported. Some of these cases have been fatal.

Table 3: Haemorrhages

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

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

Blood Disorders

Mild, transient thrombocytopenia has been reported during the first days of therapy.

Table 4: 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: Thrombocytopenia	Uncommon: Thrombocytopenia	Very common: Thrombocytosis* Common: Thrombocytopenia	Uncommon: Thrombocytopenia	Common: Thrombocytosis* Thrombocytopenia Very rare: Immuno-allergic thrombocytopenia

*Platelet increased >400 10^9/L

Hepatobiliary Disorders

Very common: Asymptomatic and reversible increases in the levels of liver enzymes (eg. transaminases) have been reported [NOTE: Liver enzymes were not assessed in the Unstable Angina Population].

Gastrointestinal Disorders

Common: Nausea, diarrhea

Other

Common: Peripheral oedema, fever

Psychiatric Disorders

Common: Confusion

Immune System Disorders

Common: Allergic reaction

Rare: Anaphylactic/ anaphylactoid reaction (see also Post-Marketing Experience)

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

Uncommon: Local irritation, skin necrosis at injection site

Investigations

Rare: Hyperkalaemia

Post-Marketing Experience

The following information relates to events observed following the marketing of CLEXANE. Voluntary reports of adverse events that have been received since market introduction (without causal relationship) that are not listed previously are cited below.

Blood and Lymphatic System Disorders

Rare cases of immuno-allergic thrombocytopenia with or without thrombosis have been reported. In some cases, thrombosis was complicated by organ infarction or limb ischaemia (see Section 4.4 - Special warnings and precautions for use).

Asymptomatic and reversible increases in platelet counts, haemorrhagic anaemia and eosinophilia have been reported.

Immune System Disorders

Anaphylactic/ anaphylactoid reactions including shock have been reported.

Metabolism Disorders

Cases of hyperkalaemia have been reported with heparins and low molecular weight heparins. Use of low molecular weight heparins over extended periods has been reported to be associated with development of osteopenia. Very rare cases of hyperlipidemia have also been reported.

Nervous System Disorders

Headaches have been reported.

Vascular Disorders

Rare: There have been rare reports of spinal or neuraxial haematomas with the concurrent use of CLEXANE and spinal/epidural anaesthesia, spinal puncture or post-operative indwelling catheters. These events have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see Section 4.4 - Special warnings and precautions for use).

Hepatobiliary Disorders

Hepatocellular liver injury and cholestatic liver injury have been reported.

Skin and Subcutaneous Tissue Disorders

Rare: Cutaneous (bullous) or systemic allergic reactions (such as pruritus, rash and urticaria), including anaphylactic/anaphylactoid reactions, may occur. In some cases discontinuation of the treatment may be necessary.

Cases of hypersensitivity cutaneous vasculitis have been reported.

Alopecia has also been reported.

Musculoskeletal and Connective Tissue Disorders

Osteoporosis following long-term therapy (greater than 3 months) has been reported.

General Disorders and Administration Site Conditions

Very rare: Pain, haematoma and mild local irritation may follow the subcutaneous injection of CLEXANE.

Hard inflammatory nodules, which are not cystic enclosures of CLEXANE, have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation.

Rare cases of skin necrosis, usually occurring at the injection site, have been reported with both unfractionated and low molecular weight heparins. These phenomena are usually preceded by purpura or erythematous plaques, infiltrated and painful. Treatment must be discontinued immediately.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Oral ingestion of CLEXANE (no reported cases) should lead to no serious consequences, taking into account the very low gastric and intestinal absorption of the product. This may be checked by carrying out a plasma assay of the anti-Xa and anti-IIa activities.

Accidental overdosage after intravenous, extracorporeal or subcutaneous administration of massive doses of CLEXANE may lead to haemorrhagic complications through anti-coagulant activity. This may be largely neutralised by the slow intravenous infusion of protamine. Particular care should be taken to avoid overdosage with protamine, as even with high doses of protamine, the anti-Xa activity of CLEXANE is never completely neutralised (maximum reversal of 60%), even though the anti-coagulant activity is neutralised. (See the prescribing information for protamine salts).

The dose of protamine depends on the dose of CLEXANE injected. If CLEXANE was administered in the previous 8 hours, 1 mg or 100 anti-heparin units of protamine neutralises the anti-IIa activity generated by 1 mg (100 IU anti-Xa activity) of CLEXANE. An infusion of 0.5 mg protamine per 1 mg of CLEXANE may be administered if CLEXANE was administered greater than 8 hours previously, or if it has been determined that a second dose of protamine is required. Protamine administration may not be required 12 hours after the CLEXANE injection. However, depending on the clinical circumstances, eg the size of the dose of CLEXANE, whether or not a therapeutic level of anticoagulation needs to be retained and whether or not the patient is actively bleeding, the administration of a reduced dose of protamine may not be advisable.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Enoxaparin sodium is a low molecular weight heparin (MW approx. 4500 D). The drug substance is the sodium salt. The molecular weight distribution is:

<2000 daltons 12 to 20%

2000 to 8000 daltons 68 to 82%

>8000 daltons ≤18%

Enoxaparin sodium is obtained by alkaline depolymerisation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterised by a 4-enopyranose uronate group at the non-reducing end. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains a 1,6 anhydro derivative on the reducing end of the polysaccharide chain.

Mechanism of action

In comparison with natural heparin CLEXANE is characterised by a clear increase in the ratio between anti-Xa and anti-IIa activities which is always greater than 4.

It has several actions on the coagulation pathway through binding to anti-thrombin III. The anti-thrombotic activity is related to inhibition of thrombin generation and inhibition of two main coagulation factors: Factor Xa and Thrombin. CLEXANE also induces a sustained release of the Tissue Factor Pathway Inhibitor *in vivo*.

In the experimental animal, CLEXANE was found to have potent anti-thrombotic properties with a minimum effect on bleeding.

Clinical trials

Hip Replacement Surgery

Two randomised single-centre clinical trials were conducted in patients undergoing hip replacement surgery to determine if extended prophylaxis with CLEXANE 40 mg SC daily, given for up to 3 weeks post hospital discharge was effective in reducing the incidence of deep vein thrombosis (DVT) as compared to placebo. All patients were initially treated with CLEXANE 40-mg SC daily, beginning up to 12 hours prior to surgery in an open-label fashion. Patients who did not exhibit venous thromboembolic disease (either by negative venography in one study or by absence of clinical signs or symptoms in the other study) at the completion of in-hospital treatment were randomised to receive extended prophylaxis with either CLEXANE (n = 221) or placebo (n = 220) post-discharge in a blinded fashion. The incidence of deep vein thrombosis (total and proximal) during extended prophylaxis was significantly lower for CLEXANE (total: 12%; proximal: 6%) compared to placebo (total: 28%; proximal: 16%) in both studies. Bleeding events were limited to minor haemorrhages which were 11% for the CLEXANE treatment group versus 3% for the placebo treatment group. The majority of the bleeding events for both groups were injection site haemorrhages (9% CLEXANE vs 2% placebo).

Thromboembolism Prophylaxis in Medical Patients

One randomised, double-blind, placebo-controlled, parallel group study was conducted to compare enoxaparin 20 mg once daily (E20), enoxaparin 40 mg once daily (E40) and placebo in the prophylaxis of VTE in patients hospitalised with acute heart failure, acute respiratory disease, acute infectious disease, acute rheumatic disorders, or acute inflammatory bowel disease. The treatment lasted 6-14 days. The primary efficacy endpoint was assessed in 866 patients – 288 placebo, 287 E20 and 291 E40 (respectively, 77.6%, 78.8% and 79.3% of those randomised to each group). The incidence of VTE was significantly lower in the E40 group (16/291, 5.5%) than in the placebo group (43/288, 14.9%), with a relative risk of 0.37 (95% CI 0.22-0.63, p = 0.0002). The incidence of VTE in the E20 group (43/287, 15%) was not significantly different from that in the placebo group, with a relative risk of 1.03 (95% CI 0.70-1.51, p = 0.90).

Unstable Angina and Non-Q-Wave Myocardial Infarction

In an international multicentre study [ESSENCE], 3171 patients enrolled at the acute phase of unstable angina or non-Q-wave myocardial infarction were randomised to receive in association with aspirin (100 to 325 mg once daily), either subcutaneous CLEXANE 1 mg/kg every 12 hours (n = 1607) or intravenous UFH adjusted based on activated partial thromboplastin time (aPPT; n = 1564). 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 median duration of treatment was 2.6 days in both groups and patients were followed up to 30 days. CLEXANE significantly decreased the incidence of recurrent angina, myocardial infarction and death, with an absolute event rate of the composite triple endpoint at day 14 of 16.6% in the CLEXANE group, compared to 19.8% in the heparin group

(p = 0.02). This represented a relative risk reduction of 16.2%, which remained statistically significant at 30 days of follow up. Furthermore, the need for revascularisation with percutaneous, transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) was significantly less frequent in the CLEXANE group (27.0% vs 32.2%, p = 0.001). The 30 day incidence of major bleeding was not significantly different between the two treatment groups (6.5% in the CLEXANE group vs 7.0% in the heparin group, p = 0.566), with an increase in minor bleeding observed in the CLEXANE group (18.4% vs 14.2%, p = 0.001), primarily constituting ecchymoses at injection sites.

Acute ST-segment Elevation Myocardial Infarction (STEMI)

In a multicentre, double-blind, double-dummy, parallel group study, 20479 patients with STEMI within 6 hours of onset and eligible to receive fibrinolytic therapy were randomised to receive either enoxaparin or UFH. All patients were also treated with aspirin for a minimum of 30 days. Study medication was administered between 15 minutes before and 30 minutes after the initiation of fibrinolytic therapy. Unfractionated heparin was administered beginning with an IV bolus of 60 IU/kg (maximum 4000 IU) and followed by an infusion of 12 IU/kg per hour (initial maximum 1000 IU per hour) that was adjusted to maintain an aPTT of 1.5 to 2.0 times the control value. The IV infusion was to be given for at least 48 hours. The enoxaparin dosing strategy was adjusted according to the patient's age and renal function. For patients younger than 75 years of age, enoxaparin was given as a single 30 mg intravenous bolus plus a 1 mg/kg SC dose followed by an SC injection of 1 mg/kg every 12 hours. For patients 75 years of age or older, the IV bolus was not given and the SC dose was reduced to 0.75 mg/kg every 12 hours. For patients with severe renal insufficiency (estimated creatinine clearance of less than 30 mL per minute), the dose was to be modified to 1 mg/kg every 24 hours. The SC injections of enoxaparin were given until hospital discharge or for a maximum of eight days (whichever came first). The mean treatment duration for enoxaparin was 6.6 days. The mean treatment duration of UFH was 54 hours.

When percutaneous coronary intervention (PCI) was performed during the study medication period, patients were to receive antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin, the PCI was to be performed on enoxaparin (no switch) using the regimen established in previous studies, i.e. no additional dosing if the last SC administration was given less than 8 hours before balloon inflation; IV bolus of 0.3 mg/kg enoxaparin if the last SC administration was given more than 8 hours before balloon inflation.

A total of 20506 patients were enrolled in the study, and 20479 patients were included in the intention to treat (ITT) population. Patients ranged in age from 20-99 years (mean age 59.8 years), with 23.5 % of patients female and 76.5% male. Race was distributed as follows: 87.2% Caucasian, 0.2% Black, 9.8% Asian and 2.8% other. Medical history included previous MI (13%), hypertension (44%), diabetes (15%) and angiographic evidence of CAD (5%). Concomitant medication included aspirin (95%), beta-blockers (86%), ACE inhibitors (78%), statins (70%) and clopidogrel (27%). The MI at entry was anterior in 43%, non-anterior in 56% and both in 1%. All patients were treated with aspirin at a dose of 75 to 325 mg for a minimum of 30 days. A fibrinolytic agent was administered to all but 4 patients, with 79.8% receiving a fibrin-specific agent (19% tenecteplase, 5% reteplase and 55% alteplase) and 20.2% receiving streptokinase. Following inclusion in this trial, 4716 patients underwent further PCI.

The primary efficacy endpoint was the composite of death from any cause or myocardial reinfarction in the first 30 days after randomisation. The efficacy data provided in the Table below show that the rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, as compared with 12.0% in the UFH group, that is a 17% reduction in the relative risk, representing an absolute risk reduction of 2.1% (P<0.001).

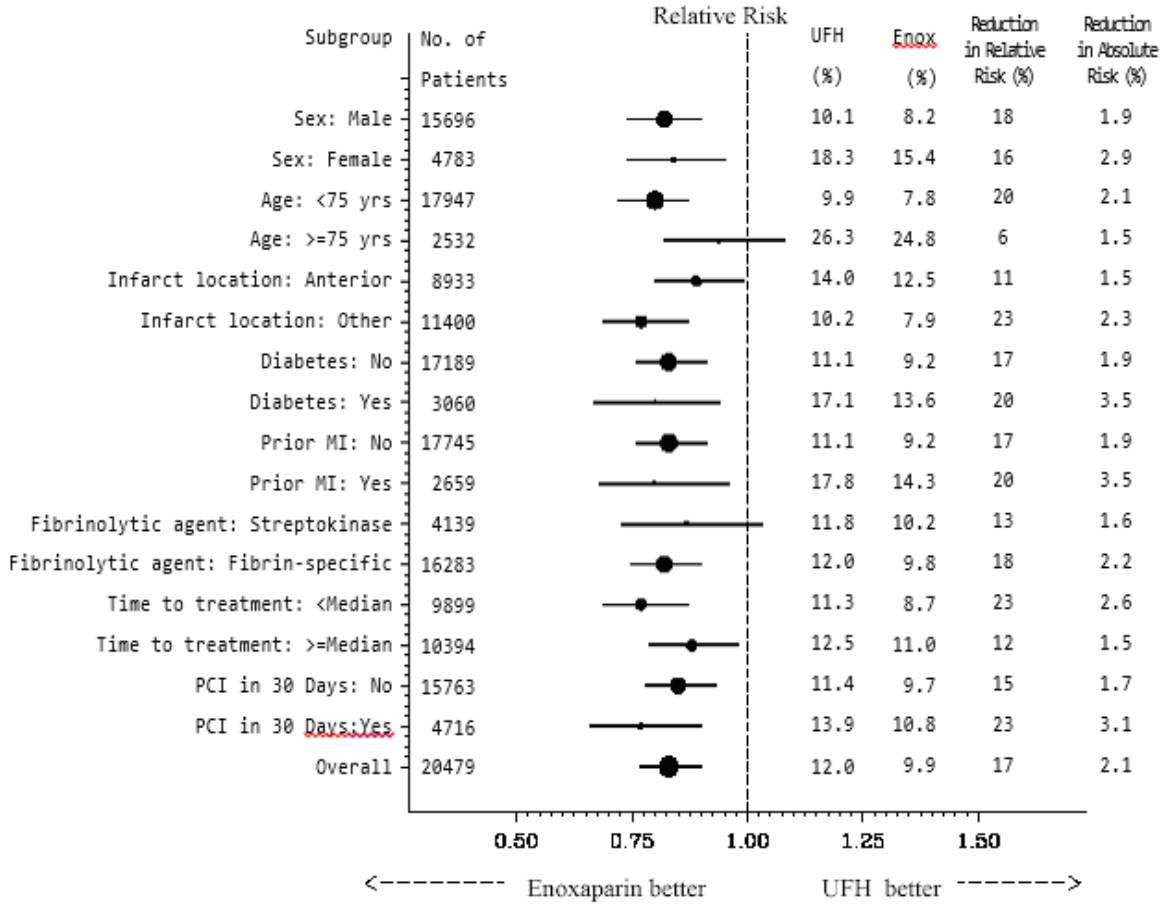
Table 5: Efficacy of Enoxaparin in the Treatment of Acute STEMI

	Enoxaparin (N = 10256)	UFH (N = 10223)	Reduction in Absolute Risk	Relative Risk (95% CI)	P Value
Outcome at 48 hours	n (%)	n (%)	(%)		
Death or Myocardial Re-infarction	478 (4.7)	531 (5.2)	0.5	0.90 (0.80 to 1.01)	0.08
Death	383 (3.7)	390 (3.8)	0.1	0.98 (0.85 to 1.12)	0.76
Myocardial Re-infarction	102 (1.0)	156 (1.5)	0.5	0.65 (0.51 to 0.84)	<0.001
Urgent Revascularisation	74 (0.7)	96 (0.9)	0.2	0.77 (0.57 to 1.04)	0.09
Death or Myocardial Re-infarction or Urgent Revascularisation	548 (5.3)	622 (6.1)	0.8	0.88 (0.79 to 0.98)	0.02
Outcome at 8 Days					
Death or Myocardial Re-infarction	740 (7.2)	954 (9.3)	2.1	0.77 (0.71 to 0.85)	<0.001
Death	559 (5.5)	605 (5.9)	0.4	0.92 (0.82 to 1.03)	0.15
Myocardial Re-infarction	204 (2.0)	379 (3.7)	1.7	0.54 (0.45 to 0.63)	<0.001
Urgent Revascularisation	145 (1.4)	247 (2.4)	1.0	0.59 (0.48 to 0.72)	<0.001
Death or Myocardial Re-infarction or Urgent Revascularisation	874 (8.5)	1181 (11.6)	3.1	0.74 (0.68 to 0.80)	<0.001
Outcome at 30 Days					
Primary efficacy endpoint (Death or Myocardial Re-infarction)	**1017 (9.9)**	**1223 (12.0)**	**2.1**	**0.83 (0.77 to 0.90)**	**<0.001**
Death	708 (6.9)	765 (7.5)	0.6	0.92 (0.84 to 1.02)	0.11
Myocardial Re-infarction	352 (3.4)	508 (5.0)	1.6	0.69 (0.60 to 0.79)	<0.001
Urgent Revascularisation	213 (2.1)	286 (2.8)	0.7	0.74 (0.62 to 0.88)	<0.001
Death or Myocardial Re-infarction or Urgent Revascularisation	1199 (11.7)	1479 (14.5)	2.8	0.81 (0.75 to 0.87)	<0.001

Note: Urgent revascularisation denotes episodes of recurrent myocardial ischaemia (without infarction) leading to the clinical decision to perform coronary revascularization during the same hospitalization. CI denotes confidence intervals.

The treatment benefits of enoxaparin, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35% reduction in the relative risk of myocardial re-infarction, as compared with UFH (P <0.0001), representing an absolute risk reduction of 0.5%. The beneficial effect of enoxaparin on the primary endpoint was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, fibrinolytic administered and time to treatment with study drug, however it is necessary to interpret such subgroup analyses with caution (see Figure 1 below).

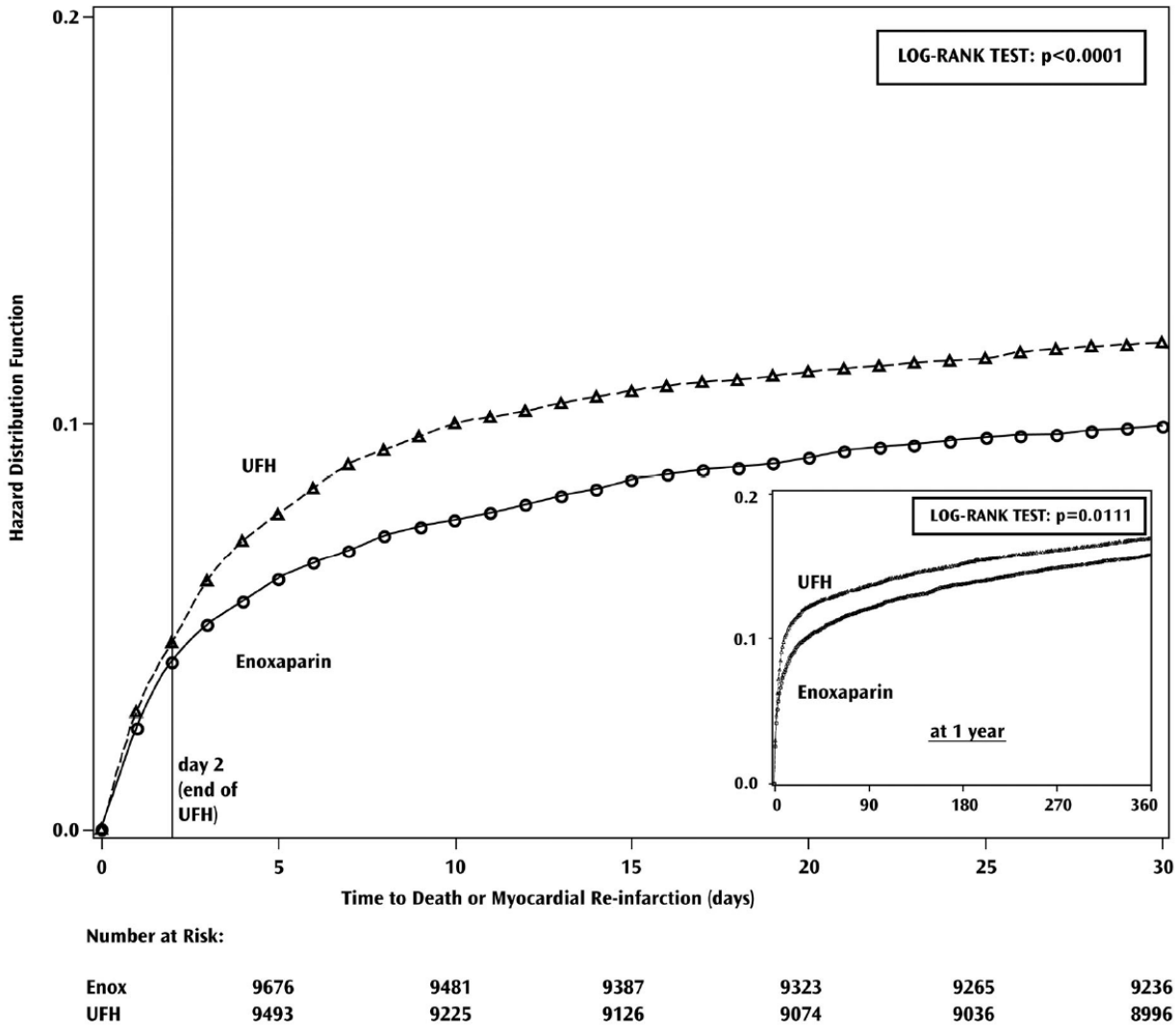
Figure 1: Relative Risks of and Absolute Event Rates for the Primary Endpoint at 30 Days in Various Subgroups



The primary efficacy endpoint was the composite of death from any cause or myocardial re- infarction in the first 30 days. The overall treatment effect of enoxaparin as compared to the UFH is shown at the bottom of the figure. For each subgroup, the circle is proportional to the number of patients and represents the point estimate of the treatment effect and the horizontal lines represent the 95% confidence intervals. Fibrin-specific fibrinolytic agents included alteplase, tenecteplase and reteplase. Time to treatment indicates the time from the onset of symptoms to the administration of study drug (median 3.2 hours). Although there was some variation in the estimate of the treatment effect of enoxaparin on the primary endpoint across the subgroups shown, all P values in tests for interaction were non significant.

The beneficial effect of enoxaparin on the primary endpoint observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2 below).

Figure 2: Kaplan-Meier plot - death or myocardial re-infarction at 30 days - ITT population



Number at Risk:

Enox	9676	9481	9387	9323	9265	9236
UFH	9493	9225	9126	9074	9036	8996

There was a significant treatment benefit of enoxaparin, as compared with UFH, in patients who underwent PCI within 30 days after randomisation (23% relative risk reduction, representing an absolute risk reduction of 3.1%) or who were treated medically (15 % relative risk reduction, representing an absolute risk reduction of 1.7%, P = 0.27 for interaction).

The rates of major haemorrhages (defined as requiring 5 or more units of blood for transfusion, or 15% drop in hematocrit or clinically overt bleeding, including intracranial haemorrhage) at 30 days were 2.1% in the enoxaparin group and 1.4% in the UFH group. The rates of intracranial haemorrhage at 30 days were 0.8% in the enoxaparin group 0.7% in the UFH group.

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 group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favour of treatment with enoxaparin, representing an absolute risk reduction of 2.1%.

Renal Impairment

A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of CLEXANE in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is increased by 20% in mild (creatinine clearance 50-80 mL/min) and 21% in moderate (creatinine clearance 30-50 mL/min) renal impairment after repeated subcutaneous 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 subcutaneous 40 mg once daily doses.

Weight

In obese subjects, after repeated subcutaneous 1.5 mg/kg daily dosing, mean AUC of anti-Xa activity is 19% higher at steady-state in obese healthy volunteers (BMI >30 kg/m^2) compared to non-obese healthy control subjects (18< BMI = <25 kg/m^2), while maximal plasma activity is not increased. There is a lower weight-adjusted clearance (L/h/kg) in obese subjects compared to non-obese subjects.

In low-weight subjects, anti-Xa exposure is 52% higher in healthy low-weight women (<45 kg but BMI >18 kg/m^2) and 27% higher in healthy low-weight men (<57 kg but BMI >18 kg/m^2) when compared to healthy normal weight subjects (<60 kg for women & >72 kg for men with BMI of 18-28 kg/m^2 for both genders). The maximal plasma activity was also increased by 45% for low-weight women and 31% for low-weight men compared to their respective normal weight controls.

Elderly

Based on the results of a pharmacokinetic analysis, the CLEXANE kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of CLEXANE.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic parameters of CLEXANE were studied from the changes in plasma anti-Xa activity.

The anti-Xa activity generated by CLEXANE does not cross the placental barrier during the second trimester of pregnancy.

Anti-Xa activity generated by CLEXANE is localised within the vascular space.

Absorption

After injection of CLEXANE by the subcutaneous route (SC), the product is rapidly and completely absorbed. The absolute bioavailability is over 90%.

Distribution

The maximum plasma activity is observed after 3 hours and is, on average, 1.6 µg/mL after the SC injection of a 20 mg dose and 3.8 µg/mL after the injection of a 40 mg dose. The anti-Xa activity, measured like that of unfractionated heparin (UFH), gives values of approximately 0.16 and 0.38 IU/mL respectively.

A 30 mg intravenous (IV) bolus immediately followed by 1 mg/kg SC provided initial peak anti-Xa levels of 1.16 IU/mL (n = 16) and an average exposure corresponding to 84% of steady-

state levels. Steady-state is achieved on the second day of treatment following continued SC dosing of 1 mg/kg every 12 hours. The aPTT (activated partial thromboplastin time) immediately after the first SC injection was 49.6 seconds. The average aPTT prolongation value on Day 1 was about 16% higher than on Day 4.

Metabolism

Metabolic breakdown of CLEXANE is slight and takes place mainly in the liver (desulphation and depolymerisation). Small amounts of the product are eliminated by the kidneys in an intact or slightly degraded form.

Excretion

The elimination of enoxaparin (based on anti-Xa activity levels) is characterised by a half-life of approximately 4.4 hours for a dose of 40 mg. At higher doses of 73.8 mg to 132.6 mg, a study has shown that anti-Xa activity levels exhibit a first phase elimination half-life of ~5 hours and a second stage elimination half-life of ~9 hours. Following a 40 mg dose, anti-Xa activity may persist in the plasma for 24 hours.

Elimination of CLEXANE at prophylactic dosages is not significantly modified in patients with mild (creatinine clearance 50-80 mL/min) to moderate (creatinine clearance 30-50 mL/min) renal insufficiency. It is slightly reduced in the elderly ($t_{½}$ = 6-7 hours). This modification has no effect on the doses or the frequency of injections, as there is no plasma accumulation in elderly subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Enoxaparin was not genotoxic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Enoxaparin sodium solution for injection also contains water for injections as an inactive ingredient.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Refer to Section 6.4 – Special precautions for storage.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not freeze CLEXANE.

CLEXANE 20 mg/0.2 mL, CLEXANE 40 mg/0.4 mL, CLEXANE 60 mg/0.6 mL, CLEXANE 80 mg/0.8 mL and CLEXANE 100 mg/1 mL injection syringes: Store for three years below 25°C.

CLEXANE FORTE (120 mg/0.8 mL, 150 mg/1 mL) injection syringes: Store for two years below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Clexane

20 mg/0.2 mL (anti-Xa: 2,000 IU) ready-to-use, prefilled syringes, 1s[#] and 10s

40 mg/0.4 mL (anti-Xa: 4,000 IU) ready-to-use, prefilled syringes, 1s[#], 10s and 15s[#]

60 mg/0.6 mL (anti-Xa: 6,000 IU) ready-to-use, prefilled syringes with graduated markings, 1s[#], 6s[#], 10s and 15s[#]

80 mg/0.8 mL (anti-Xa: 8,000 IU) ready-to-use, prefilled syringes with graduated markings, 1s[#], 6s[#], 10s and 15s[#]

100 mg/1 mL (anti-Xa: 10,000 IU) ready-to-use, prefilled syringes with graduated markings, 2s[#]and 10s

Clexane (with safety lock system)

20 mg/0.2 mL (anti-Xa: 2,000 IU) ready-to-use, prefilled syringes, 1s[#] and 10s

40 mg/0.4 mL (anti-Xa: 4,000 IU) ready-to-use, prefilled syringes, 1s[#], 10s and 15[#]s

60 mg/0.6 mL (anti-Xa: 6,000 IU) ready-to-use, prefilled syringes with graduated markings, 1s[#], 6s[#], 10s and 15[#]s

80 mg/0.8 mL (anti-Xa: 8,000 IU) ready-to-use, prefilled syringes with graduated markings, 1s[#], 6s[#], 10s and 15[#]s

100 mg/1 mL (anti-Xa: 10,000 IU) ready-to-use, prefilled syringes with graduated markings, 2s[#] and 10s

Clexane Forte Syringes

120 mg/0.8mL (anti-Xa: 12,000 IU) ready-to-use, prefilled syringes with double graduated markings, 8s[#], 10s and 15s[#]

150 mg/1 mL (anti-Xa: 15,000 IU) ready-to-use, prefilled syringes with the double graduated markings, 8s[#], 10s and 15s[#]

Clexane Forte Syringes (with safety lock system)

120 mg/0.8mL (anti-Xa: 12,000 IU) ready-to-use, prefilled syringes with double graduated markings 8s[#], 10s and 15s[#]

150 mg/1 mL (anti-Xa: 15,000 IU) ready-to-use, prefilled syringes with the double graduated markings 8s[#], 10s and 15s[#]

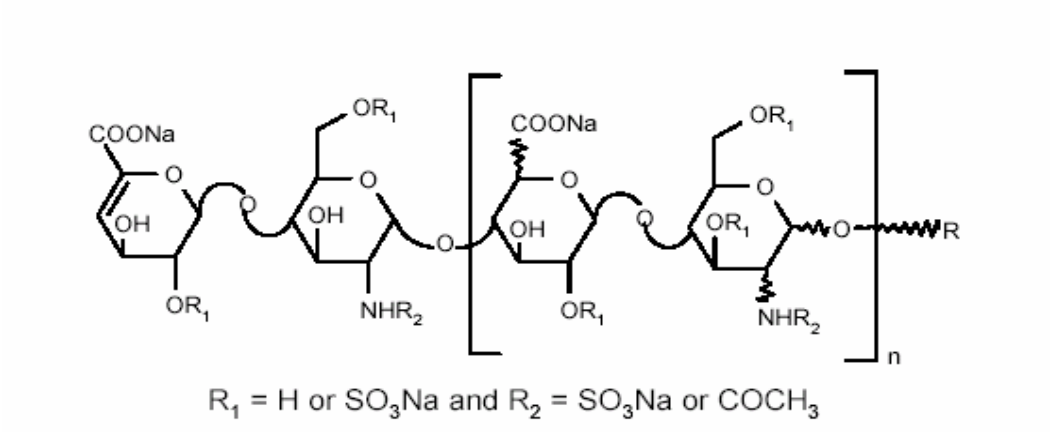
[#] Not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

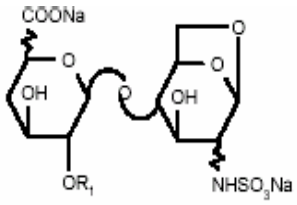
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

R	X = 15 to 25%		n= 0 to 20
	100 - X	H	n =1 to 21

X = Percent of polysaccharide chain containing 1, 6 anhydro derivative on the reducing end

CAS number

9041-08-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

12 February 1993

10 DATE OF REVISION

23 December 2025

*References to “CLEXANE” refer to both CLEXANE and CLEXANE FORTE

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Addition of new safety lock system