PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

CLEXANE® 20 (Solution for injection in prefilled syringes)

CLEXANE® 40 (Solution for injection in prefilled syringes)

CLEXANE® 60 (Solution for injection in prefilled syringes)

CLEXANE® 80 (Solution for injection in prefilled syringes)

CLEXANE® 100 (Solution for injection in prefilled syringes)

CLEXANE® 300 (Solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CLEXANE 20: Enoxaparin sodium 20 mg per 0,2 ml

CLEXANE 40: Enoxaparin sodium 40 mg per 0,4 ml

CLEXANE 60: Enoxaparin sodium 60 mg per 0,6 ml

CLEXANE 80: Enoxaparin sodium 80 mg per 0,8 ml

CLEXANE 100: Enoxaparin sodium 100 mg per 1,0 ml

CLEXANE 300: Per multidose vial: Enoxaparin sodium 300 mg and benzyl alcohol (preservative) 1,5 % *m/v* in 3,0 ml water for-injections.

(sugar free)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

CLEXANE 20, CLEXANE 40, CLEXANE 60, CLEXANE 80 and CLEXANE 100:

Solution for injection in prefilled syringes:

Clear, colourless to pale yellow solution.

CLEXANE 300:

Solution for injection:

Clear and practically free from particles, colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- To reduce the risk of post-operative venous thrombosis and embolism in moderate and high-risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery.
- To reduce the risk of venous thromboembolism in patients bedridden due to debilitating medical illnesses.
- Treatment of deep venous thrombosis with or without pulmonary embolism. Safety of home treatment for this indication has not been established.
- To reduce the risk of ischaemic complications of unstable angina or non-Q-wave myocardial infarction, within 24 hours of onset, combined with aspirin (100 - 325 mg daily) for 8 days, or until stabilisation, revascularisation or discharge from hospital.
- To reduce the risk of thrombus formation in extracorporeal circulation during haemodialysis.
- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

4.2 Posology and method of administration

Posology

To reduce the risk of post-operative venous thrombosis and embolism in moderate and high risk surgical patients:

Individual thromboembolic risk for patients can be estimated using validated risk stratification model.

Moderate Risk Patients: In general surgery, 20 mg (0,2 ml) once daily by subcutaneous injection. The first injection should be given 2 hours pre-operatively.

Treatment is continued for as long as the risk of thromboembolism persists; in general, from 7 to 10 days after surgery or as long as there is a risk of venous thromboembolism and until the patient is ambulatory.

High Risk Patients: In orthopaedic or general surgery including cancer surgery, 40 mg (0, 4 ml) once daily by subcutaneous injection. The first injection should be given 12 hours pre-operatively.

If there is a need to initiate CLEXANE earlier than 12 hours pre-operatively to reduce risk (e.g. high risk patient waiting for a deferred orthopaedic surgery), the last injection should be administered no later than 12 hours prior to surgery and resumed 12 hours after surgery.

- For patients who undergo major orthopaedic surgery with a high venous thromboembolism risk, an extended thromboprophylaxis up to 5 weeks is recommended.
- For patients with a high venous thromboembolism (VTE) risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks is recommended.

For special recommendations concerning dosing intervals for spinal/epidural anaesthesia and percutaneous coronary revascularisation procedures; see section 4.4.

To reduce the risk of venous thromboembolism in medical patients:

The recommended dose of CLEXANE is 40 mg once daily by subcutaneous injection. CLEXANE treatment is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days.

Treatment of deep vein thrombosis with or without pulmonary embolism:

A dose of 1 mg/kg should be given subcutaneously every 12 hours.

Oral anticoagulant therapy should be initiated when appropriate and CLEXANE treatment should be continued until a therapeutic anticoagulant effect has been achieved (International Normalised Ratio 2 to 3). CLEXANE treatment is usually prescribed for between 5 and 10 days.

To reduce the risk of ischaemic complications of unstable angina or non-Q-wave myocardial infarction:

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

Treatment with CLEXANE 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.

To reduce the risk of extracorporeal thrombus during haemodialysis:

The recommended dose is 1 mg/kg of CLEXANE.

For patients with a high risk of haemorrhage, the dose should be reduced to 0,5 mg/kg for double vascular access or 0,75 mg/kg for single vascular access.

During haemodialysis, CLEXANE should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 0,5 to 1 mg/kg may be given.

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI):

The recommended dose of CLEXANE is a single IV bolus of 30 mg plus a 1 mg/kg subcutaneous dose, followed by 1 mg/kg administered subcutaneously every 12 hours (maximum 100 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining doses). For dosage in patients > 75 years of age, refer to the section on 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 and maintained on an appropriate dose once daily, unless contraindicated.

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

For patients managed with Percutaneous Coronary Intervention (PCI): If the last CLEXANE subcutaneous administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last subcutaneous administration was given more than 8 hours before balloon inflation, an IV bolus of 0,3 mg/kg of CLEXANE should be administered.

Paediatric population:

The safety and efficacy of enoxaparin sodium in paediatric population have not been established (see section 4.3).

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 subcutaneous every 12 hours (maximum 75 mg for the first two doses only, followed by 0,75 mg/kg dosing for the remaining doses). For other indications, no dose reduction is necessary in the elderly, unless kidney function is impaired (see section 4.4 – Haemorrhage in the elderly; section 5.2 – Elderly and section 4.2 – Renal impairment).

The efficacy of CLEXANE injection in the elderly (≥ 65 years) was similar to that seen in younger patients (< 65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of CLEXANE injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when CLEXANE injection was administered at doses of 1,5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of CLEXANE injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving CLEXANE injection. Other clinical experience (including post-marketing surveillance and literature reports) has not revealed additional differences in the safety of CLEXANE injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (< 45 kg) and those predisposed to decreased renal function should be considered (see section 5.2 and section 4.4).

Renal impairment:

In the absence of safety data on dosages more than 80 mg daily and delayed elimination in patients with severe renal impairment, dosages of more than 60 mg daily should be used with caution. Special safety vigilance is warranted in patients with severe renal impairment, as there may be an increased bleeding tendency due to the renal failure.

See sections 4.4 and 5.2 – Renal impairment.

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 CLEXANE exposure is significantly increased in this patient population.

The following dosage adjustments are recommended 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 30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC twice daily	1 mg/kg SC once daily 30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC once daily

Elderly patients > 75 years of age (for acute STEMI indication only)

Standard dosing: 0,75 mg/kg SC twice daily without initial bolus	Severe renal impairment: 1 mg/kg SC once daily without initial bolus

The following dosage adjustments are recommended for prophylactic dosage ranges:

Standard dosing: 40 mg SC once daily 20 mg SC once daily	Severe renal impairment: 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 dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised.

Spinal/epidural anaesthesia

For patients receiving spinal/epidural anaesthesia see section 4.4, Warnings Spinal/epidural anaesthesia.

Method of administration

Subcutaneous injection:

CLEXANE is administered by subcutaneous injection for the prevention of venous thromboembolic disease; treatment of deep vein thrombosis; treatment of unstable angina and non-Q-wave myocardial infarction and treatment of acute ST-segment Elevation Myocardial Infarction.

IV bolus injection:

For acute ST-segment Elevation Myocardial Infarction, treatment is to be initiated with a single IV bolus injection immediately followed by a subcutaneous injection.

Arterial line injection:

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

CLEXANE must never be injected intramuscularly.

The prefilled disposable syringe is ready for immediate use.

When using CLEXANE vials, the volume to be injected should be measured precisely with a graduated syringe fitted with an appropriate needle for subcutaneous injection.

Subcutaneous injection technique:

Injections should be made preferably when the patient is lying down. CLEXANE is administered by deep subcutaneous injection. Do not expel the air bubble from the syringe before injecting to avoid the loss of medicine, when using the 20 mg and 40 mg prefilled syringes. The administration should be alternated between the left and right anterolateral or posterolateral abdominal wall.

Safety device*:* The prefilled syringes fitted with an automatic safety device avoid accidental needle pricks after injecting. When the protective cap is removed off the needle, a drop may appear at the end of the needle. If so, remove it before injecting the medicine by lightly tapping the body of the syringe with the needle pointing down. The prefilled syringe is ready to use. Do not press on the plunger to

expel any air bubbles before administering the injection. The injection must be given with the patient preferably lying down. The whole length of the needle should be introduced perpendicularly, not from the side, into a skin fold held between the thumb and index finger. This skin fold should be held throughout the injection. Do not rub the injection site after administration. The safety device is automatically activated once the plunger is fully depressed, thus completely protecting the used needle and without causing discomfort to the patient. Activation of the safety device is only possible if the plunger is fully depressed. The safety device can only be activated once the syringe is completely empty.

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

For intravenous injection, the multiple-dose vial should be used. CLEXANE should be administered through an intravenous line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of CLEXANE with other medicines, 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 medicine. CLEXANE may be safely administered with normal saline solution (0,9 %) or 5 % dextrose in water. No additional bolus dose is needed if the last administration of CLEXANE was less than 8 hours before balloon inflation.

Do not use the multidose vial for more than 28 days after first use.

4.3 Contraindications

- hypersensitivity to CLEXANE, heparin or its derivatives including other Low Molecular Weight Heparins
- history of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (also see section 4.4)
- heparin-associated thrombocytopenia

- hypersensitivity to benzyl alcohol
- active major bleeding and conditions with a high risk of uncontrolled haemorrhage including recent haemorrhagic stroke; patients at risk include those with haemorrhagic blood disorders, thrombocytopenia, peptic ulcers, cerebrovascular disorders, infective endocarditis, and severe or uncontrolled hypertension
- safety and efficacy in children has not been established. **The multiple-dose formulation contains benzyl alcohol as a preservative and should not be used in neonates. The administration of medicines containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome"**

4.4 Special warnings and precautions for use

CLEXANE should be used with care in the presence of severe liver dysfunction.

CLEXANE should be used in reduced dosages in patients with severe kidney dysfunction (creatinine clearance less than 30 ml/min).

Do not administer by the intramuscular route.

Spinal/Epidural anaesthesia:

There have been cases of intraspinal haematomas reported with the concurrent use of CLEXANE and spinal/epidural anaesthesia resulting in long-term or permanent paralysis.

The risk is greater with higher CLEXANE dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional medicines affecting haemostasis such as NSAIDs see section 4.5). 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, placement and removal of the catheter is best performed when the anticoagulant effect of CLEXANE is low, however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Neuraxial techniques should be avoided in patients administered a dose of CLEXANE 2 hours pre-operatively (general surgery).

Placement or removal of a catheter should be delayed for at least 12 hours after administration of lower doses (20 mg once daily or 40 mg once daily) of enoxaparin, and at least 24 hours after the administration of higher doses (0,75 mg/kg twice daily, 1 mg/kg twice daily, or 1,5 mg/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 0,75 mg/kg twice-daily dose or the 1 mg/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 < 30 ml/minute, additional considerations are necessary because elimination of enoxaparin is more prolonged (see section 4.2: Severe renal impairment); consider doubling the timing of placement or removal of a

catheter, at least 24 hours for the lower prescribed dose of enoxaparin (20 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day).

Should the medical practitioner decide to administer anticoagulation in the context of epidural/spinal anaesthesia or lumber puncture, 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 medical practitioner 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.

Patients with Artificial Heart Valves:

In patients with artificial heart valves, CLEXANE should only be used if regular Factor-Xa activity can be monitored.

General:

Low Molecular Weight Heparins such as CLEXANE should not be used interchangeably since they differ in their manufacturing processes, molecular masses, specific anti-Xa activities, units and dosage. This results in differences in pharmacokinetics and associated biological activities {e.g. anti-thrombin (IIa) activity, and platelet interactions}.

Special attention and compliance with the instructions for use specific to each proprietary medicinal product is therefore required.

Heparin-induced thrombocytopenia:

Use of CLEXANE in patients with a history of immune mediated HIT within the past 100 days or in the presence of circulating antibodies is contraindicated (see section 4.3). Circulating antibodies may persist several years.

CLEXANE is to be used with extreme caution in patients with a history (more than 100 days) of heparin-induced thrombocytopenia without circulating antibodies. 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.

Monitoring of platelet counts:

The risk of antibody-mediated heparin-induced thrombocytopenia also exists with CLEXANE. Should thrombocytopenia occur, it usually appears between the 5th and 21st day following the beginning of CLEXANE treatment. Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with CLEXANE and then regularly thereafter during treatment. In practice, if 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.

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 acute ST-segment elevation myocardial infarction, adherence to the intervals recommended between CLEXANE doses is essential. 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 CLEXANE is to be continued, the

next scheduled dose should be given no sooner than 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or haematoma formation.

Mechanical prosthetic heart valves:

The use of CLEXANE has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Prosthetic heart valve thrombosis and fatalities have been reported in patients with mechanical prosthetic heart valves who have received CLEXANE for thromboprophylaxis.

Pregnant women with mechanical prosthetic heart valves:

The use of CLEXANE for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. There have been post-marketing reports of fatal valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving CLEXANE for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism. CLEXANE is not recommended for this use.

Haemorrhage:

Bleeding may occur at any site (see section 4.8).

If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted.

CLEXANE injection should be used with caution in conditions with increased potential for bleeding, such as:

- history of peptic ulcer
- impaired haemostasis
- recent ischaemic stroke
- uncontrolled severe arterial hypertension

- diabetic retinopathy
- recent neuro- or ophthalmologic surgery
- concomitant use of medications affecting haemostasis see section 4.5).

Haemorrhage in the elderly:

Elderly patients are at an increased risk for bleeding complications with both the prophylactic and therapeutic dosage ranges of CLEXANE. Careful clinical monitoring is advised (see section 4.2 – Elderly and section 5.2 - Elderly).

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 dose adjustment is recommended in patients with moderate (creatinine clearance 30–50 ml/min) and mild (creatinine clearance 50–80 ml/min) renal impairment, careful clinical monitoring is advised (see sections 4.2 and 5.2 – Renal impairment).

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 monitoring is advised in these patients (see section 5.2 - Weight).

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. These patients should be observed carefully for signs and symptoms of thromboembolism.

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. Therefore, standard clotting tests cannot be done to monitor treatment.

Inter-individual variations in bleeding and coagulation times may occur even when identical dosages are used.

At higher doses than used for prophylaxis, 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 CLEXANE antithrombotic activity and therefore are unsuitable and unreliable for monitoring CLEXANE activity.

4.5 Interaction with other medicines and other forms of interaction

It is recommended that medicines which affect haemostasis should be discontinued prior to CLEXANE therapy unless strictly indicated, such as:

- systemic salicylates, acetylsalicylic acid and NSAIDs including ketorolac and diclofenac,
- dextran 40, ticlopidine and clopidogrel,
- systemic glucocorticoids,
- thrombolytics and anticoagulants,
- other anti-platelet agents including glycoprotein IIb/IIIa antagonists.

If the combination cannot be avoided, CLEXANE should be used with careful clinical and laboratory monitoring.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established. Also see section 4.4: Mechanical prosthetic heart valves and Pregnant women with mechanical prosthetic heart valves.

As there are no adequate and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, CLEXANE should be used during pregnancy only if the medical practitioner has established a clear need.

Breastfeeding

Mothers receiving CLEXANE should not breastfeed their infants.

4.7 Effects on ability to drive or use machines

CLEXANE has no effect on the ability to drive and operate machines.

4.8 Undesirable effects

Summary of safety profile

In clinical studies, haemorrhages, thrombocytopenia and thrombocytosis were the most commonly reported reactions (see section 4.4 and 'Description of selected adverse reactions below').

Tabulated summary list of adverse reactions

Adverse reactions observed in clinical studies and reported in post-marketing experience (* indicates reactions from post-marketing experience) are detailed below.

The following frequency rating has been used:

Very common: (>1/10); Common: (>1/100, <1/10); Uncommon: (>1/1000, <1/100); Rare: (>1/10 000, <1/1000); Very rare: (<1/10 000), including rare isolated cases.

Blood and the lymphatic system disorders

Common: Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis

Rare: Eosinophilia*, cases of immuno-allergic thrombocytopenia* with thrombosis (in some of them thrombosis was complicated by organ infarction or limb ischaemia (see section 4.4))

Immune system disorders

Common: allergic reaction

Rare: anaphylactic or anaphylactoid reaction including shock*

Nervous system disorders

Common: Headache*

Vascular disorders

Rare: Cases of spinal/neuraxial haematoma* have been reported with the concurrent use of CLEXANE as well as spinal/epidural anaesthesia or spinal puncture. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis.

Hepato-biliary disorders

Very common: hepatic enzymes increase (mainly transaminase levels > 3 times the upper limit of normality)

Uncommon: Hepatocellular liver injury*

Rare: Cholestatic liver injury*

Skin and subcutaneous tissue disorders

Common: urticaria, pruritus, erythema

Uncommon: bullous dermatitis

Rare: cutaneous vasculitis*, skin necrosis* usually occurring at the injection site (these phenomena are usually preceded by purpura or erythematous plaques, infiltrated and painful). Treatment with CLEXANE must be discontinued, if
cutaneous vasculitis or skin necrosis occurs. Injection site nodules* (inflammatory nodules which were not cystic enclosure of enoxaparin), alopecia*

Musculoskeletal and connective tissue disorders

Rare: osteoporosis* following long-term therapy (longer than 3 months)

General disorders and administration site conditions

Common: injection site haematoma, injection site pain, other injection site reaction (such as injection side oedema, haemorrhage, hypersensitivity, inflammation, mass, pain or reaction)

Uncommon: local irritation, skin necrosis at injection site

Investigations

Rare: hyperkalaemia.

Description of selected adverse reactions

Haemorrhages

Haemorrhages were the most commonly reaction, including major and fatal haemorrhages. Haemorrhage may occur even without the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis.

MedDRA	Prophylaxis in	Prophylaxis in	Treatment in	Treatment in	Treatment in

system organ class	surgical patients	medical patients	patients with DVT with or without PE	patients with unstable angina and non-Q-wave MI	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.

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 G/L

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8, or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Signs and symptoms:

Accidental overdosage with CLEXANE after intravenous, extracorporeal or subcutaneous administration may lead to haemorrhagic complications.

Management:

Antidote and treatment

The anticoagulant effects may be partially neutralised by the slow intravenous injection of protamine. However, even with high doses of protamine, the anti-Xa activity of CLEXANE is never completely neutralised (maximum about 60 %).

Not more than 50 mg of protamine sulphate should be injected for any one dose.

Further treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Enoxaparin sodium belongs to the medicine class A 8.2 Anticoagulants.

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

Enoxaparin sodium is a low molecular weight heparin which has a greater antithrombotic (anti-Factor Xa) activity than a thrombolytic effect (anti-Factor IIa activity) *in vivo*.

It is well absorbed after subcutaneous injection, with a half-life of the anti-Factor Xa activity of 4,5 hours. This is increased to 6,7 hours in the elderly.

5.2 Pharmacokinetic properties

The anti-Factor Xa activity disappears within 24 hours after administration of the recommended dose. Heparins are metabolised in the liver by the enzyme heparinase. The heparin half-life is significantly prolonged in patients with cirrhosis of the liver.

A 30 mg IV bolus immediately followed by a 1 mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1,16 IU/ml and average exposure corresponding to 88 % of steady-state levels. Steady-state is achieved on the second day of treatment.

Characteristics in special populations:

Elderly: Since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see section 4.4 – Haemorrhage in the elderly, section 4.2– Elderly, and Renal impairment below).

Renal impairment: A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 ml/min) and moderate (creatinine clearance 30-50 ml/min) renal impairment after repeated 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 (see section 4.4 – Renal impairment & section 4.2 – Renal impairment).

Weight: After repeated subcutaneous 1,5 mg/kg once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady-state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-

obese control subjects, while A_{max} is not increased. There is a lower weight-adjusted clearance in obese subjects with subcutaneous dosing.

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 – Low weight).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CLEXANE 20, CLEXANE 40, CLEXANE 80, CLEXANE 60 and CLEXANE 100:

Water for injections

CLEXANE 300:

Benzyl alcohol

Water for injections

6.2 Incompatibilities

SC injection:

Do not mix with other products.

IV (Bolus) Injection (for acute STEMI indication only):

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

Prefilled syringes: 3 years

Multidose vial: 2 years

Do not use the multidose vial for more than 28 days after first use.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze or refrigerate.

Prefilled syringes: discard any unused portion.

Multidose vial: for storage conditions after first opening of the, see Section 6.3.

6.5 Nature and contents of container

CLEXANE 20: 0,2 ml solution for injection in a 0,5 ml prefilled syringe with a safety device, in packs of 6 or 10.

CLEXANE 40: 0,4 ml solution for injection in a 0,5 ml prefilled syringe with a safety device in packs of 6 or 10.

CLEXANE 60: 0,6 ml solution for injection in a 1 ml prefilled syringe with a safety device in packs of 6 or 10.

CLEXANE 80: 0,8 ml solution for injection in a 1 ml prefilled syringe with a safety device in packs of 6 or 10.

CLEXANE 100: 1 ml solution for injection in a 1 ml prefilled syringe with a safety device in packs of 6 or 10.

CLEXANE 300: 3 ml solution for injection in a single multidose vial.

6.6 Special precautions for disposal and other handling

The prefilled disposable syringe is ready for immediate use. For method of administration see section 4.2.

Use only clear, colourless to yellowish solutions.

Each prefilled syringe is for single use only.

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

011 256 3700

8 REGISTRATION NUMBER(S)

CLEXANE 20: A39/8.2/0079

CLEXANE 40: X/8.2/42

CLEXANE 60: 31/8.2/0480

CLEXANE 80: 31/8.2/0481

CLEXANE 100: 31/8.2/0482

CLEXANE 300: 32/8.2/0122

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

CLEXANE 20: 17 February 2006

CLEXANE 40: 02 August 1991

CLEXANE 60; CLEXANE 80 and CLEXANE 100: 17 March 1999

CLEXANE 300: 25 May 1999

10 DATE OF REVISION OF THE TEXT

13 October 2023