SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

CLEXANE® 20 (Injection)

CLEXANE® 40 (Injection)

CLEXANE® 60 (Injection)

CLEXANE® 80 (Injection)

CLEXANE® 100 (Injection)

CLEXANE® 300 (Injection)

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

Benzyl alcohol (preservative) 1,5 % m/v

Water for injection to 3,0 ml

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION:

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.

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 (refer to Special Precautions – Haemorrhage in the elderly; DOSAGE AND DIRECTIONS FOR USE – Elderly & Pharmacological Action - Renal impairment).

Renal impairment: A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 ml/min) and moderate (creatinine clearance 30-50 ml/min) renal impairment after repeated 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 (refer to Special Precautions – Renal impairment & DOSAGE AND DIRECTIONS FOR USE – 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 (refer to Special Precautions – Low weight).

INDICATIONS:

- To reduce the risk of post-operative venous thrombosis and embolism in high-risk patients (e.g. orthopaedic surgery) and moderate-risk patients (e.g. abdominal 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).

CONTRAINDICATIONS:

- hypersensitivity to CLEXANE, heparin or its derivatives including other Low Molecular Weight Heparins
- heparin-associated thrombocytopenia
- CLEXANE should not be given to patients who are actively bleeding from any site
- hypersensitivity to benzyl alcohol
- CLEXANE should be avoided in patients at risk of haemorrhage; patients at risk include those with haemorrhagic blood disorders, thrombocytopenia, peptic ulcers, cerebrovascular disorders, infective endocarditis, and severe or uncontrolled hypertension
- safety in pregnancy and lactation has not been established
- 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"**
- safety and efficacy in patients with prosthetic heart valves has not been established. There have been case reports of failed therapy and consequent clot formation and obstruction of prosthetic valves.

WARNINGS:

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 (refer to interactions with other medicinal products or other forms of interaction). The risk also appears to be increased by traumatic or repeated neuraxial puncture.

Placement and removal of the catheter is best performed when the anticoagulant effect of CLEXANE is low. 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 10-12 hours after administration of DVT prophylactic doses of CLEXANE, whereas patients receiving higher doses of CLEXANE (1 mg/kg twice daily or 1,5 mg/kg once daily) will require longer delays (24 hours). The subsequent CLEXANE dose should be given no sooner than 2 hours after catheter removal.

Should the medical practitioner decide to administer anticoagulation in the context of epidural/spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Patients should be instructed to inform their 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.

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:
CLEXANE is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia, with or without thrombosis. The risk of heparin-induced thrombocytopenia may persist for several years. If a history of heparin-induced thrombocytopenia is suspected, the decision to use CLEXANE in such a case must be made only in consultation with an expert in the field.

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 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or haematoma formation.

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 valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving CLEXANE for thromboprophylaxis. CLEXANE is not recommended for this use.

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. 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.

INTERACTIONS:

It is recommended that agents 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.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established. (Refer to WARNINGS – Pregnant women with mechanical prosthetic heart valves and Special Precautions – Mechanical prosthetic heart valves).

As a precaution, lactating mothers receiving CLEXANE should be advised to avoid breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:

To reduce the risk of post-operative venous thrombosis and embolism:

High Risk Patients: In orthopaedic surgery, 40 mg (0,4 ml) once daily by subcutaneous injection.

The first injection should be given 12 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 until the patient is ambulatory.

Continued therapy with 40 mg once daily for 3 weeks following the initial therapy has been proven to be beneficial in total hip replacement.

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.
For special recommendations concerning dosing intervals for spinal/epidural anaesthesia and percutaneous coronary revascularisation procedures; refer to WARNINGS section.

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:

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.

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 (refer to Special Precautions – Haemorrhage in the elderly; Pharmacological Action – Elderly and DOSAGE AND DIRECTIONS FOR USE – 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 (refer to Pharmacological Action and Special Precautions).

Impaired renal function:
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.

Renal impairment:
Refer to Special Precautions – Renal impairment and Pharmacological Action – 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	1 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	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)

0.75 mg/kg SC twice daily without initial bolus	1 mg/kg SC once daily without initial bolus

The following dosage adjustments are recommended for prophylactic dosage ranges:

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

20 mg SC once daily 20 mg SC once daily

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

Moderate and mild renal impairment: Although no 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.

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.

Administration:

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.

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects*:*

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 lymphatic system disorders

Common: during CLEXANE therapy, 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. The origin of the bleeding should be investigated and appropriate

treatment instituted. Transient, asymptomatic thrombocytopenia has been reported during the first days of therapy.
Rare: asymptomatic and reversible increases in platelet counts have been reported. Gastrointestinal bleeding, haematuria and haemarthrosis have been reported.
Very rare: major bleeding including retroperitoneal and intra-cranial bleeding has been reported. Some of these cases have been fatal. When neuraxial anaesthesia (epidural/spinal anaesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with CLEXANE for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by use of indwelling epidural catheters for administration of analgesia, or the concomitant use of agents affecting haemostasis such as NSAIDs, platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture. Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

Immune system disorders
Rare: cases of severe immuno-allergic thrombocytopenia, with or without arterial thrombosis, have been reported. In some cases, thrombosis was complicated by organ infarction or limb ischaemia (refer to Special Precautions - Monitoring of platelet counts).
Very rare: cutaneous (bullous eruptions) or systemic allergic reactions including anaphylactoid reactions have occurred. In some cases discontinuation of treatment may be necessary.

Skin and subcutaneous tissue disorders
Very rare: cases of hypersensitivity cutaneous vasculitis have been reported.

General disorders and administration site conditions
Common: pain, haematoma and mild local irritation may follow the subcutaneous injection of CLEXANE.
Rare: hard inflammatory nodules, which are non-cystic enclosures of CLEXANE, have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation.
Very rare: cases of skin necrosis at the injection site have been reported with CLEXANE. This phenomena is usually preceded by purpura or erythematous plaques, infiltrated and painful. Treatment with CLEXANE must be discontinued.

Hepatobiliary disorders

Common: asymptomatic and reversible increases in liver enzyme levels have been reported.

Others

Isolated cases of hepatitis, eosinophilia, neutropenia and leukopenia have been reported with the use of CLEXANE.

Special Precautions:

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.

Haemorrhage:

Bleeding may occur at any site (refer to Side effects).
If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted.

Standard clotting tests cannot be done to monitor treatment because unlike unfractionated heparin, CLEXANE in therapeutic doses does not modify coagulation time or platelet function and neither does it prolong APTT or TT.

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 (refer to INTERACTIONS).

Mechanical prosthetic heart valves:

The use of CLEXANE has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received CLEXANE 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 prosthetic heart valves may be at higher risk for thromboembolism (refer to WARNINGS – Pregnant women with mechanical prosthetic heart valves).

Haemorrhage in the elderly:

Elderly patients may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical monitoring is advised (refer to DOSAGE AND DIRECTIONS FOR USE – Elderly & Pharmacological Action - 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 (refer to DOSAGE AND DIRECTIONS FOR USE – Renal impairment & Pharmacological Action – 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 (refer to Pharmacological Action - Weight).

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Severe bleeding with CLEXANE, usually caused by accidental overdosage, may be reduced by slow intravenous administration of protamine sulphate.

1 mg of protamine sulphate is stated to inhibit the effects of 1 mg (100 units) of CLEXANE.

Such doses of protamine sulphate should completely neutralise the anti-thrombin effect of CLEXANE but not the anti-Factor Xa effect (maximum of 60 % anti-Factor Xa activity is neutralised).

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

Further treatment is symptomatic and supportive.

IDENTIFICATION:

CLEXANE 20 Injection: Clear, colourless to pale yellow solution.

CLEXANE 40 Injection: Clear, colourless to pale yellow solution.

CLEXANE 60 Injection: Clear, colourless to pale yellow solution.

CLEXANE 80 Injection: Clear, colourless to pale yellow solution.

CLEXANE 100 Injection: Clear, colourless to pale yellow solution.

CLEXANE 300 Injection: Clear and practically free from particles, colourless to slightly yellow solution.

PRESENTATION:

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

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

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

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

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

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

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Do not freeze or refrigerate. Discard any unused portion.

Keep out of reach of children.

REGISTRATION NUMBERS:

CLEXANE 20 Injection: A39/8.2/0079

CLEXANE 40 Injection: X/8.2/42

CLEXANE 60 Injection: 31/8.2/0480

CLEXANE 80 Injection: 31/8.2/0481

CLEXANE 100 Injection: 31/8.2/0482

CLEXANE 300 Injection: 32/8.2/0122

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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