SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORM:

NOXFIBRA 20 (Solution for injection)

NOXFIBRA 40 (Solution for injection)

NOXFIBRA 60 (Solution for injection)

NOXFIBRA 80 (Solution for injection)

NOXFIBRA 100 (Solution for injection)

COMPOSITION:

Active ingredient:

Noxfibra 20 pre-filled syringe contains enoxaparin sodium 20 mg/0,2 mℓ (equivalent to 2 000 IU Anti Factor Xa).

Noxfibra 40 pre-filled syringe contains enoxaparin sodium 40 mg/0,4 mℓ (equivalent to 4 000 IU Anti Factor Xa).

Noxfibra 60 pre-filled syringe contains enoxaparin sodium 60 mg/0,6 mℓ (equivalent to 6 000 IU Anti Factor Xa).

Noxfibra 80 pre-filled syringe contains enoxaparin sodium 80 mg/0,8 mℓ (equivalent to 8 000 IU Anti Factor Xa).

Noxfibra 100 pre-filled syringe contains enoxaparin sodium 100 mg/mℓ (equivalent to 10 000 IU Anti Factor Xa).

Excipients:

Water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Enoxaparin is a low molecular weight heparin which, potentiates the actions of antithrombin III an endogenous inhibitor of blood coagulation.

Enoxaparin acts primarily by increasing antithrombin III-mediated inhibition of the formation and activity of factor Xa (anti Factor Xa). This activity, in turn, reduces thrombin generation. These actions decrease thrombin-mediated events in coagulation, including the conversion of fibrinogen to fibrin, thereby inhibiting fibrin clot formation. Unlike unfractionated heparin, which has an anti-factor Xa (antithrombotic) to anti-factor IIa (anticoagulant) activity ratio of approximately 1 to 1, enoxaparin has an anti-factor Xa to anti-factor IIa activity ratio of approximately 3 to 1.

Enoxaparin's higher ratio of antithrombotic to anticoagulant activity is thought to result in an antithrombotic effect equivalent to that of unfractionated heparin with a lower risk of bleeding. However, it has not been consistently demonstrated that the risk of bleeding is lower with enoxaparin than with unfractionated heparin. Enoxaparin also decreases inhibition of platelet function and disrupts vascular permeability to a lesser extent than does unfractionated heparin.

Pharmacokinetic properties:

Enoxaparin is measured by its anticoagulant mechanism that is expressed as anti-factor Xa activity (IU/mg).

Absorption:

Enoxaparin sodium is well absorbed after subcutaneous injection with bioavailability of 92 %.

Peak anti-factor Xa concentration occurs at 3 to 5 hours after SC administration.

A 30 mg IV bolus immediately followed by a 1 mg/kg sub-cutaneous (SC) dose 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.

Distribution and biotransformation:

The volume of distribution (Vd) of enoxaparin sodium anti-factor Xa is 5 to 6 litres.

The anti-Factor Xa activity disappears within 24 hours after administration of the recommended dose.

Enoxaparin is metabolised in the liver by depolymerisation and disulfation.

Elimination:

Elimination of enoxaparin sodium is primarily renal with a half-life of the anti-factor Xa activity of 4,5 hours. This is increased to 6,7 hours in the elderly. Total body clearance after an intravenous dose is approximately 26 mℓ/min and 15 mℓ/min. After subcutaneous (SC) administration. The clearance is decreased approximately 30 % in patients with severe renal failure.

Characteristic in special populations:

Elderly:

Since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see "WARNINGS AND SPECIAL PRECAUTIONS – Haemorrhage in the elderly", "DOSAGE AND DIRECTIONS FOR USE – Elderly" and "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 presented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50 to 80 mℓ/min) and moderate (creatinine clearance 30 to 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 "WARNINGS AND SPECIAL PRECAUTIONS – Renal impairment" and "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 to 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 "WARNINGS AND SPECIAL PRECAUTIONS – Low weight").

INDICATIONS:

NOXFIBRA is indicated:

- 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 vein 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 to 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 NOXFIBRA, heparin or its derivatives including other Low Molecular Weight Heparins.
- Heparin-associated thrombocytopenia.
- NOXFIBRA should not be given to patients who are actively bleeding from any site.
- NOXFIBRA 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 (see “PREGNANCY AND LACTATION”).
- Safety and efficacy in children has not been established.
- 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 the prosthetic valves.
- Use for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves.

WARNINGS AND SPECIAL PRECAUTIONS:

Spinal/ Epidural anaesthesia:

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

The risk is greater with higher NOXFIBRA dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional medicines affecting haemostasis such as NSAIDs (see “INTERACTIONS”). 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 NOXFIBRA is low. Neuraxial techniques should be avoided in patients who have been administered a dose of NOXFIBRA 2 hours pre-operatively (general surgery).

Placement and removal of a catheter should be delayed for 10 – 12 hours after administration of DVT prophylactic doses of NOXFIBRA, whereas patients receiving higher doses of NOXFIBRA (1 mg/kg twice daily or 1,5 mg/kg once daily) will require longer delays (24 hours). The subsequent NOXFIBRA 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 NOXFIBRA should not be used interchangeably since they may 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.

Hyperkalaemia related to hypoaldosteronism has been reported in patients treated with low-molecular-weight heparins, such as NOXFIBRA.

Heparin-induced thrombocytopenia:

NOXFIBRA 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 NOXFIBRA in such 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 NOXFIBRA 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 NOXFIBRA injection.

If the treatment of NOXFIBRA 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.

Laboratory tests:

At doses used for prophylaxis of venous thromboembolism, NOXFIBRA 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 NOXFIBRA antithrombotic activity and therefore use unsuitable and unreliable for monitoring NOXFIBRA activity.

Haemorrhage:

Bleeding may occur at any site (see “SIDE EFFECTS”).

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

These include major haemorrhages, reported at most in 4.2 % of the patients (surgical patients). Some of these cases have been fatal.

In surgical patients, haemorrhage complications were considered major:

- If the haemorrhage caused a significant clinical event.
- If accompanied by haemoglobin decrease ≥ 2 g/dℓ or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.

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

Target anti-factor Xa ranges for therapeutic doses have been well defined in previous studies. For twice daily and once daily dosing of subcutaneous enoxaparin, peak anti-factor Xa levels of between 0.6 to 1.0 IU/mℓ and 1.0 to 2.0 IU/mℓ have been suggested respectively. Ranges between Low Molecular Weight Heparins (LMWH) may be sufficiently similar to aim for a standardized target range. However, there are significant differences in target levels between various LMWHs at therapeutic doses.

NOXFIBRA 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 medicines affecting haemostasis (see “INTERACTIONS”).

Mechanical prosthetic heart valves:

The use of NOXFIBRA has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves.

Fatalities of prosthetic heart valve thromboses have been reported in patients with mechanical prosthetic heart valves who received enoxaparin sodium for thromboprophylaxis (see "CONTRAINDICATIONS").

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 (see "DOSAGE AND DIRECTIONS FOR USE – Elderly" and "PHARMACOLOGICAL ACTION – Elderly").

Renal impairment:

In patients with renal impairment, there is an increase in exposure of NOXFIBRA which increases the risk of bleeding.

Since exposure of NOXFIBRA 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 to 50 mℓ/min) and mild (creatinine clearance 50 to 80 mℓ/min) renal impairment, careful clinical monitoring is advised (see "DOSAGE AND DIRECTIONS FOR USE – Renal impairment" and "PHARMACOLOGICAL ACTION – Renal impairment").

Low weight:

An increase in exposure of NOXFIBRA with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (below 45 kg) and low-weight men (below 57 kg) which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in patients (see "PHARMALOGICAL ACTION – Weight").

Monitoring of platelet counts:

The risk of antibody-mediated heparin-induced thrombocytopenia also exists with NOXFIBRA.

Should thrombocytopenia occur, it usually appears between the 5th and 21st day following the beginning of NOXFIBRA treatment.

Therefore it is recommended that the platelet counts be measured before the initiation of therapy with NOXFIBRA 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), NOXFIBRA treatment must be immediately discontinued and the patient switched to another therapy.

Effects on ability to drive and use machines:

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

INTERACTIONS:

It is recommended that medicines which affect haemostasis should be discontinued prior to NOXFIBRA 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 medicines including glycoprotein IIb/ IIIa antagonists.

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

PREGNANCY AND LACTATION:

Safety of NOXFIBRA in pregnancy and lactation has not been established (see “WARNINGS AND SPECIAL PRECAUTIONS”)

Women receiving NOXFIBRA should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:

Do not administer by intramuscular route.

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 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 (see "WARNINGS AND SPECIAL PRECAUTIONS").

To reduce the risk of venous thromboembolism in medical patients:

The recommended dose of NOXFIBRA is 40 mg once daily by subcutaneous injection. NOXFIBRA treatment is prescribed for a minimum of 6 days and continued until the return of 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 NOXFIBRA should be continued until a therapeutic anticoagulant effect has been achieved (International Normalised Ratio 2 to 3). NOXFIBRA 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 NOXFIBRA is 1 mg/kg every 12 hours by subcutaneous injection, administered concurrently with aspirin (100 to 325 mg once daily).

Treatment with NOXFIBRA 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 NOXFIBRA.

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, NOXFIBRA 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 NOXFIBRA 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, in this section.

When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), NOXFIBRA 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 NOXFIBRA treatment is 8 days or until hospital discharge, whichever comes first.

For patients managed with Percutaneous Coronary Intervention (PCI):

If the last NOXFIBRA 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 NOXFIBRA should be administered.

Elderly:

For treatment of acute ST-segment Elevation Myocardial Infarction in the elderly patient > 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 “WARNINGS AND SPECIAL PRECAUTIONS” – Haemorrhage in the elderly,

"PHARMACOLOGICAL ACTION" – Elderly and "DOSAGE AND DIRECTIONS FOR USE" – Renal impairment).

The efficacy of NOXFIBRA 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 of 40 mg once a day doses of NOXFIBRA injection was employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when NOXFIBRA injection was administered at doses of 1,5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of NOXFIBRA injection-associated bleeding increased with age.

Serious adverse events increased with age for patients receiving NOXFIBRA injection. Other clinical experience (including post-marketing surveillance and literature reports) has not revealed additional differences in the safety of NOXFIBRA 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 "PHARMACOLOGICAL ACTION" and "WARNINGS 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 renal failure.

Renal impairment:

Refer to "WARNINGS AND 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 NOXFIBRA exposure is significantly increased in this patient population.

Table 1: The following dosage adjustments are recommended for therapeutic dosage ranges:

Standard dosing:	***Severe renal impairment:***
1 mg/kg SC twice 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 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

Table 2: Elderly patients > 75 years of age (for acute STEMI indication only):

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

Table 3: The following dosage adjustments are recommended for prophylactic dosage ranges:

Standard dosage:	***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 to 50 mℓ/min) and mild (creatinine clearance 50 to 80 mℓ/min) renal impairment, careful clinical monitoring is advised.

Subcutaneous injection:

NOXFIBRA 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:

NOXFIBRA must never be injected intramuscularly.

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

When using NOXFIBRA 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. NOXFIBRA 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 pre-filled syringes. The administration should be alternated between the left and right anterolateral or posterolateral abdominal wall.

Safety device:

The pre-filled 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 pre-filled 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. The 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. NOXFIBRA should be administered through an intravenous line. It should not be mixed or co-administered with other medicines. To avoid the possible mixture of NEXFIBRA 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 NOXFIBRA to clear the port of medicine. NOXFIBRA 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 the first use.

SIDE EFFECTS:

The following frequency rating has been used:

Frequent: (> 1/10); (> 1/100, <1/10);

Less frequent: (> 1/1000, <1/100); (> 1/10 000, <1/1000); (<1/10 000), including rare isolated cases.

Blood and lymphatic system disorders:

Frequent **:** Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis.

Less frequent **:** Eosinophilia,

Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia

Immune system disorders:

Frequent **:** Allergic reaction

Less frequent **:** Anaphylactic/Anaphylactoid reactions including shock

Nervous system disorders:

Frequent **:** Headache.

Vascular disorders:

Less frequent **:** Spinal haematoma* (or neuraxial haematoma). These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis

Hepato-biliary disorders:

Frequent *:* Hepatic enzyme increases (mainly transaminases > 3 times the upper limit of normality)

Less frequent *:* Hepatocellular liver injury

Cholestatic liver injury

Skin and subcutaneous tissue disorders:

Frequent *:* Urticaria, pruritus, erythema

Less frequent *:* Bullous dermatitis, Alopecia, Cutaneous vasculitis*, skin necrosis* usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful).

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

Musculoskeletal, connective tissue and bone disorders:

Less frequent *:* Osteoporosis

General disorders and administration site conditions:

Frequent *:* Injection site haematoma, injection site pain, other injection site reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction)

Less frequent *:* Local irritation, skin necrosis at injection site

Investigations:

Less frequent *:* Hyperkalaemia

Description of selected adverse reactions

Haemorrhages:

During NOXFIBRA 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 initiated.

Thrombocytopenia and thrombocytosis:

Transient, asymptomatic thrombocytopenia, has been reported during the first days of therapy.
Asymptomatic and reversible increases in platelet counts have been reported. Gastrointestinal bleeding, haematuria and haemarthrosis have been reported. 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 NOXFIBRA 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 medicines 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.
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 (see “WARNINGS AND SPECIAL PRECAUTIONS – monitoring of platelets”).

Injection site:

Hard inflammatory nodules which are non-cystic enclosures of NOXFIBRA have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation. Cases of skin necrosis at the injection site have been reported with NOXFIBRA. This phenomena is usually preceded by purpura and erythematous plaques, infiltrated and painful. Treatment with NOXFIBRA must be discontinued.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Severe bleeding with NOXFIBRA, 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 NOXFIBRA.

Such doses of protamine sulphate should completely neutralise the anti-thrombin effect of NOXFIBRA 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:

Noxfibra is a clear, colourless solution (clear liquid) that is free from visible particulate matter.

PRESENTATIONS:

Noxfibra 20	:	is a 0,2 mℓ (20 mg/0,2 mℓ) solution for injection, packed in 0,5 mℓ clear and colourless type I glass pre-filled syringes with chlorobutyl rubber stopper fitted with injection needle and an automatic safety device. The plunger rod is white in colour.
Noxfibra 40	:	is a 0,4 mℓ (40 mg/0,4 mℓ) solution for injection, packed in a 0,5 mℓ clear and colourless type I glass pre-filled syringes with chlorobutyl rubber stopper fitted with injection needle and an automatic safety device. The plunger rod is yellow in colour.
Noxfibra 60	:	is a 0,6 mℓ (60 mg/0,6 mℓ) solution for injection, packed in a 1 mℓ clear and colourless type I glass pre-filled syringes with chlorobutyl rubber stopper fitted with injection needle and an automatic safety device. The plunger rod is orange in colour.
Noxfibra 80	:	is a 0,8 mℓ (80 mg/0,8 mℓ) solution for injection, packed in a 1 mℓ clear and colourless type I glass pre-filled syringes with chlorobutyl rubber stopper fitted with injection needle and an automatic safety device. The plunger rod is brown in colour.
Noxfibra 100	:	is a 1 mℓ (100 mg/mℓ) solution for injection, packed in a 1 mℓ clear and colourless type I glass pre-filled syringes with chlorobutyl rubber stopper fitted with injection needle and an automatic safety device. The plunger rod is black in colour.

The pre-filled syringes are packed into an outer cardboard carton.

NOXFIBRA pre-filled syringes are packed in 10’s.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Do not freeze.

For single, one-time use only. Any unused solution should be discarded.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

Noxfibra 20	:	52/8.2/0495
Noxfibra 40	:	52/8.2/0496
Noxfibra 60	:	52/8.2/0497
Noxfibra 80	:	52/8.2/0498
Noxfibra 100	:	52/8.2/0499

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

Sandoz SA (Pty) Ltd[1]

72 Steel Road

Spartan

Kempton Park, 1619

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