FRAXIPARINE™/FRAXIPARINE FORTE™/FRAXODI™

Indications

- The treatment of thromboembolic disorders.
- The prevention of clotting during haemodialysis.
- The treatment of unstable angina and non-Q wave myocardial infarction.

Dosage and Administration

- Those in high risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure), hospitalised in intensive care unit.

FRAXIPARINE FORTE and FRAXODI [Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU/ml)]

The usual site for subcutaneous injection is on the right or left side of the abdominal wall, but the thigh may be used if necessary. The injection should not be given into fatty tissue. The injection should be given to dry skin, which should be held gently but firmly until injection has been completed. The injection site should not be rubbed.

Subcutaneous injection technique:

- Pinch the skin firmly between thumb and forefinger. Insert the needle at an angle of 90° to the skin and inject the medication slowly, followed by gentle pressure to disperse the contents of the syringe. The needle should be held at an angle of about 15° to ensure even dispersal of the drug.

Dosage and Treatment

- For thromboembolic disorders:
  - Adults: 0.4 ml (3,800 anti-Xa IU) administered subcutaneously twice daily (every 12 hours) for a usual duration of 10 days. The dose should be adjusted for body weight according to the table below, which is based on a target dose of 86 anti-Xa IU per kg body weight.
  - Post-operative days onwards:
    - Up to 50 kg: 2,850 anti-Xa IU administered subcutaneously 2 to 4 hours before surgery, and then once daily on subsequent days. Treatment should be continued for at least seven days, and throughout the risk period, until the patient is ambulant.
    - 50-59 kg: 3,800 anti-Xa IU
    - 60-69 kg: 4,750 anti-Xa IU
    - 70-79 kg: 5,700 anti-Xa IU
    - 80-89 kg: 6,650 anti-Xa IU
    - ≥ 90 kg: 7,600 anti-Xa IU

- For unstable angina and non-Q wave myocardial infarction:
  - Adults: 0.4 ml (3,800 anti-Xa IU) administered subcutaneously twice daily (every 12 hours) for 5 to 10 days. Treatment should be continued for at least seven days, and throughout the risk period, until the patient is ambulant.

- For haemodialysis:
  - Adults: 5 ml of solution equivalent to 47,500 anti-Xa IU administered subcutaneously twice daily (every 12 hours) for a usual duration of 10 days. The dose should be adjusted for body weight according to the table below, which is based on a target dose of 86 anti-Xa IU per kg body weight.

- For prophylaxis of thromboembolic disorders:
  - Adults: 0.3 ml (2,850 anti-Xa IU) administered subcutaneously 2 to 4 hours before surgery, and then once daily on subsequent days. Treatment should be continued for at least seven days, and throughout the risk period, until the patient is ambulant.

Volume injected (ml) Anti-Xa IU

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Volume injected (ml)</th>
<th>Anti-Xa IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.7 ml</td>
<td>2,850</td>
</tr>
<tr>
<td>60-69</td>
<td>0.8 ml</td>
<td>3,800</td>
</tr>
<tr>
<td>70-79</td>
<td>0.9 ml</td>
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</tbody>
</table>

Contraindications

- Hypersensitivity to nadroparin or any of the excipients of nadroparin
- Severe renal impairment (see Warnings and Precautions and Pharmacokinetics)
- History of thrombocytopenia with nadroparin
- Disseminated intra-vascular coagulation.
- Worsening of the initial thrombosis while on therapy
- History of peptic ulceration or other organic lesion likely to bleed
- Severe arterial hypertension
- Hepatic failure
- Immediate or delayed hypersensitivity reactions to heparin (either standard or low molecular weight heparin), treatment with nadroparin is contraindicated.

Warnings and Precautions

- Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients with raised plasma renin activity.
- Hyperkalaemia is usually transient and mild, but may be severe and life-threatening in patients with renal impairment.

- Heparin can cause the following adverse effects:
  - Haemorrhage
  - Thrombocytopenia
  - Disseminated intravascular coagulation
  - Adverse reactions similar to those caused by heparin

- Heparin has not been studied in children below 18 years of age, and it is not recommended for use in children.

- Heparin can cause the following serious adverse reactions:
  - Anaphylactoid reactions
  - Intravascular coagulation
  - Thrombocytopenia

- Heparin can cause the following less serious adverse reactions:
  - Mild local injection site reactions
  - Gastrointestinal disorders

- Heparin can interact with other drugs and cause the following adverse effects:
  - Anticoagulants: Increased anticoagulant effect
  - Non-steroidal anti-inflammatory drugs: Increased risk of bleeding

- The frequency of adverse reactions is related to the dose and duration of therapy.
Studies in animals have not shown any teratogenic or foetotoxic effects. However, there is only limited clinical data concerning transplacental passage of nadroparin treatment with nadroparin on fertility.

The needle shield of the pre-filled syringe may contain dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals. Cutaneous Necrosis has been reported very rarely. It is preceded by purpura or infiltrated or painful erythematous blotches, with or without general signs. In such cases, treatment should be immediately discontinued.

The use of protamine sulphate should be considered only in serious cases. It largely neutralises the anti-coagulant effect of nadroparin, but the duration of anticoagulation therapy may be prolonged. The platelet count and other tests of haemostatic function should be monitored carefully. The use of protamine sulphate may be followed by a partial thrombocytopenia, especially in patients with pre-existing thrombocytopenia. However, protamine is not generally effective in reversing the anticoagulant effect of unfractionated heparin.

Very rare: Cutaneous necrosis, usually occurring at the injection site.

Haemorrhage is the major clinical sign of subcutaneous or intravenous overdosage. The platelet count and other tests of haemostatic function should be monitored carefully. The use of protamine sulphate may be followed by a partial thrombocytopenia, especially in patients with pre-existing thrombocytopenia. However, protamine is not generally effective in reversing the anticoagulant effect of unfractionated heparin.

Haemorrhagic manifestations at various sites, more frequent in patients with other risk factors (see Contraindications and Interactions).

Metabolism and nutrition disorders

Reproductive system and breast disorders

Blood and lymphatic system disorders

Nadroparin should be visually inspected for any particulate matter and discoloration before use. If any visual change is observed, the product should not be used.

The injection is given in the side of the lower stomach (figure 1). Alternate the left and right side of the stomach at each injection.

In a clinical study investigating the pharmacokinetics of nadroparin administered intravenously in patients with varying renal function and body weight, the bioavailability of nadroparin was found to be almost complete (around 88%). After i.v. injection, the peak plasma anti-Xa level is reached within less than 10 minutes, and the half-life is around 2 hours (see Pharmacokinetics: Renal Impairment below). Wide inter-individual variability was observed in the study. In subjects with severe renal impairment (creatinine clearance <15 ml/min), both bioavailability and half-life were reduced. In patients undergoing surgery, the metabolism of nadroparin may be influenced by other medication and individual factors. Therefore, the concomitant prescription of a neuraxial blockade and of an anti-coagulant therapy should be decided after careful individual benefit / risk assessment. In patients already treated with anti-coagulants, the benefits of a neuraxial blockade should be carefully weighed against the risks involved.

Pharmacokinetics: Renal Impairment

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Therefore, the use of nadroparin during pregnancy is not advised, unless the therapeutic benefits outweigh the possible risks. Nadroparin should be used with caution in patients with a history of thromboembolic disease, or with a family history of thrombophilia.

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