**Compositions**

One 0.3 ml (3,200 I.U.aXa) subcutaneous prefilled-syringe contains:

**Active ingredient**: Parnaparin 3,200 I.U.aXa.

**Excipient**: Water for injection

One 0.4 ml (4,250 I.U.aXa) subcutaneous prefilled-syringe contains:

**Active ingredient**: Parnaparin 4,250 I.U.aXa.

**Excipient**: Water for injection

**Pharmaceutical Form and Packagings**

Box of six 0.3 ml subcutaneous prefilled-syringes (3,200 I.U.aXa)

Box of six 0.4 ml subcutaneous prefilled-syringes (4,250 I.U.aXa)

**Pharmacotherapeutics Class**

Heparinics-Antitrombotics

**Mechanisms of Activity**

is an antithrombotic product with a quick and long-lasting activity and is active in thromboembolic disease treatment. Fluxum, unlike heparin, has the property of keeping its antithromboembolic disease treatment. Fluxum, unlike heparin, has the property of keeping its antithrombotic activity separate from its anticoagulant activity. In fact, the ratio between its antithrombotic activity, measured by activated actor x assay, and its anticoagulant activity, represented by apt and TT values, is higher than 4, always in comparison with heparin; this ration may be considered as a therapeutic or safety index. Fluxum, unlike heparin, has no platelet pro-aggregant activity.

**Pharmacokinetic Properties**

On average Fluxum shows its maximum anti-Xa activity plasma peak 3 hours after subcutaneous administration and has a plasma half-life of about 6 hours; the anti-Xa activity persists in the blood for about 20 hours after a single injection; these characteristics make a single daily dose possible. Fluxum is mainly distributed in the blood, where it carries out its action, and it is probably subject to a disappearance phenomenon due to endothelial and/or transendothelial uptake, like heparin. It has a hepatic and renal metabolism and is excreted through urinary route.

**Preclinical Safety Data**

Fluxum is virtually devoid of acute and chronic toxicity and mutagenic activity, and does not interfere with the reproductive function and embryonal development in experimental models.

**Therapeutic Indications**

Prophylaxis deep venous thrombosis (DVT) in general and orthopaedic surgery. Treatment of venous disorders of thrombotic aetiology.

**Contraindications**

The use is generally unadvisable during pregnancy and lactation. Positive medial history of
thrombocytopenia with FLUXUM (also see “Special precaution for use”). Occurrence or tendencies towards hemorrhaging linked with haemostatic disturbance, with the exception of consumption coagulopathy not linked with heparin. Organ injuries with risk of bleeding (peptic ulcer, retinopathies, hemorrhagic syndrome). Acute bacterial endocarditis (with the exception of those relating to mechanical prostheses). Haemorrhagic cerebrovascular accidents. Allergy to the product. Severe nephropathies and pancreatopathies, severe arterial hypertension, severe cranioencephalic traumas (post-operative period). Therapeutical treatment with K antivitamins. Relative contra-indications: association with ticlopidine, salicylates or NSAIDs, antiplatelet agents (dipyridamole, sulphirazone, etc).

**SPECIAL PRECAUTIONS FOR USE**

FLUXUM must not be administered intramuscularly. Biological monitoring: perform a platelet count before the treatment and then twice a week; if lengthy treatment is foreseen, this frequency of monitoring must be kept up for at least the first month, after which the monitoring can be less frequent.

If there are records of thrombocytopenia as a consequence of treatment with another heparin, particular attention must be paid to the clinical state and the platelet count should be carried out every day.

If thrombocytopenia arises with classical heparin (non fractionated) substitution with a low molecular weight heparin is a possible solution.

In this case daily surveillance of platelet number is necessary and the treatment must be interrupted as soon as possible; in fact there have been reports of cases where the initial thrombocytopenia has persisted also with molecular weight heparin.

In vitro platelet aggregation tests are only of indicative value. It is advisable to get in contact with a specialized team.

Treatment: to be used with caution in case of liver failure, renal failure, arterial hypertension, medical history of gastro-intestinal ulcer or any other organic lesions which are susceptible of bleeding, or chorioretinal vascular diseases. To be used with caution in the postoperative period of brain or spinal cord surgery.

Low molecular weight heparins differ in production method, molecular weight and their specific activity. It is therefore not advisable to change from one brand product to another during treatment.

**INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION**

*Unadvisable combination:*

- Acetylsalicylic acid and other salicylates (systemic route)
  - Increase in risk of haemorrhage (inhibition of platelet function and injury to the gastroduodenal mucosa caused by salicylates)
  - Use other substance for an analgetic or antipyretic effect.

- NSAIDs (systemic route)
  - Increase in risk of haemorrhage (inhibition of platelet function and injury to the gastroduodenal mucosa caused by non-steroidal anti-inflammatory drugs).
  - It is not possible to avoid the associations, set up careful clinical and biological surveillance.

- Ticlopidien
  - Increase in risk of haemorrhage (inhibition of platelet function caused by ticlopidine).
  - It is unadvisable to associate it with strong doses of heparin.

The association with low doses of heparin (heparin prophylaxis) must be carried out under a strict clinical and biological
- Antiplatelet agents (dipyridamole, sulphinpyrazone, etc.)
  Increase in risk of haemorrhage (inhibition of platelet function)

Combination which require precautions for use:
- Oral anticoagulant agents
  Strengthening of the anticoagulant action. Heparin alters the dosage of the protrombin rate.
  Replacing heparin with oral anticoagulants:
  a. increase the clinical surveillance
  b. in order to check their it is advisable to perform blood-drawings before the administration of heparin, incase it is discontinuous, or preferably, use a regent which is not sensitive to the heparin.

- Glucocorticoids (by systemic route)
  Worsening of the risk of haemorrhage characteristic of glucocorticoid therapy (gastric mucosa, vascular fragility), with high doses or protracted treatments (more than days).
  The association should be justified, increase the clinical surveillance.

- Dextran (parenterally)
  Increase in risk of haemorrhage (inhibition of platelet function). Adjust the heparin posology so as not to exceed a hypocoagulability of 1.5 times the reference value both during the association and after suspending the dextran.
  In case of concomitant administration of ascorbic acid, antihistaminics, digitalis, tetracyclines or phenothiaxines, an inhibition of the product activity may occur.

WARNINGS
The risk of toxic effects on foetus and/or suckling following Parnaparin administration cannot be excluded and therefore the use of Fluxum in pregnancy and/or during lactation should be restricted, according to doctor’s judgment, in cases of absolute necessity.
KEEP OUT OF THE REACH OF CHILDREN.

POSOLOGY AND METHOD ADMINISTRATION
FLUXUM should be administered subcutaneously
- In the prophylaxis of deep venous thrombosis (DVT) in general surgery and orthopaedic surgery the following dosage is recommended:

  General surgery:
  One subcutaneous injection of 0.3 ml (3,200 I.U.aXa) 2 hours before the operation.
  Subsequently every 24 hours for at least 7 days. Haemocoagulation tests are not necessary.

  Patients with a high thromboembolic risk and in orthopaedic surgery:
  One subcutaneous injection of 0.4 ml (4,250 I.U.aXa) 12 hours before and 12 hours after the operation, then one injection a day during the postoperative period.
  The duration of the treatment is of at least 10 days.
  - In the treatment of deep venous thrombosis (DVT) the subcutaneous administration may preceded by a 3-5 day period of intravenous treatment by slow infusion.
Deep venous thrombosis (DVT):
Two subcutaneous injections of 0.6 ml (6,400 I.U.aXa) every day. The treatment must be effected for at least 7-10 days.
This treatment may be preceded for 3-5 days by treatment with 12,800 I.U.aXa administered via i.v. with slow infusion.
After the acute phase the treatment can continue with 0.6 ml (6,400 I.U.aXa) day or with 0.4 ml (4,250 I.U.aXa) day administered subcutaneously for further 10-20 days.

Post-phlebitic syndrome, chronic venous insufficiency:
One subcutaneous injection 0.3 ml (3,200 I.U.aXa) every 24 hours, depending on the severity of the case.
The duration of the treatment is of at least 30 days.

Acute superficial thrombophlebitis, varicophlebitis:
One subcutaneous injection 0.4 ml (4,250 IU.aXa) or 0.3 ml (3,200 I.U.aXa) every 24 hours, depending on the severity of the case.
The duration of the treatment is of at least 20 days.

INJECTION TECHNIQUE
The injection must be made in the subcutaneous tissues of the upper external quadrants of the buttocks, alternating the right side with the left, or of the anterolateral and posterolateral abdominal girdle.
The needle must be inserted, for its whole length, perpendicularly (not tangentially) into the thickness of a cutaneous fold formed between the operator’s thumb and forefinger.
The fold must be held till the end of the injection.

OVERDOSE AND ANTIDOTE
The special device containing the product makes an overdose unlikely; however should an overdosage occur accidentally, effects linked with its anticoagulant activity (bleeding) may occur, which are not normally present at therapeutic doses.
These effects can be neutralized by administering protamine sulphate intravenously; 0.6 ml of protamine sulphate are necessary in order to inhibit 0.1 ml of FLUXUM.

UNDESIRABLE EFFECTS
Slight haemorrhagic manifestations mainly linked with preexistent risk factors, such as organic lesions with haemorrhagic tendencies or with iatrogenic effects (see “Contraindications” and “Interactions with other medicaments and other forms of interaction”).
Rare cases of thrombocytopenia, occasionally severe (see “Special precautions for use”).
Rare cases of cutaneous necrosis, usually localized at the injection site, which are observed both with classical heparins and low molecular weight heparins. These phenomena are preceded by the occurrence of purpura or infiltrated and painful erythematous plaques with or without general symptoms. In these cases it is necessary to suspend the treatment immediately.
Exceptionally, slight haematomas occur at the injection site. Rare occurrences of cutaneous or general allergy. Increase in transaminases.
Inform the doctor if other undesirable effects, not reported in this leaflet, occur. Attention: see the expiry date reported on the outer pack. Do not use the medical speciality after such date.

STORAGE
Store below 25°C
Shelf life : 3 years

“Bersumber babi”
“Sumber bahan baku obat harus diinformasikan dokter kepada pasien (Drug sources should be informed to the patient by doctor)”

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

Manufactured by:
ALFA WASSERMANN S.p.A
Alanno Scalo (PE) – Italy

Imported by:
PT. PRATAPA NIRMALA
Tangerang - Indonesia