PHAREPA 5000 I.U./1ML SOLUTION FOR SUBCUTANEOUS AND INTRAVENOUS INJECTION, AMPOULES
PHAREPA 25000 I.U./5ML SOLUTION FOR INTRAVENOUS INJECTION, AMPOULES-VIALS

B01AB01 **Heparin Sodium**

COMPOSITION
PHAREPA 5000 I.U./1ml for subcutaneous and intravenous use:
Each 1 ml ampoule contains:
ACTIVE INGREDIENT: heparin sodium 5000 I.U
EXCIPIENTS: Water for injection
PHAREPA 25000 I.U./5ml for intravenous use:
Each 5 ml ampoule contains:
ACTIVE INGREDIENT: heparin sodium 25000 I.U
EXCIPIENTS: Water for injection
Each 5 ml vial contains:
ACTIVE INGREDIENT: heparin sodium 25000 I.U
EXCIPIENTS: Methyl p-oxybenzoate; Propyl p-oxybenzoate; Sodium chloride; Water for injection

PACK SIZE:
- 10 ampoules of 5000 I.U/1 ml solution for subcutaneous and intravenous injection
- 1 vial of 25.000 I.U./ 5 ml solution for intravenous injection
- 5 vials of 25.000 I.U./ 5 ml solution for intravenous injection
- 10 ampoules of 25.000 I.U./ 5ml solution for intravenous injection

PHARMACOTHERAPEUTIC CATEGORY
Antithrombotic/anticoagulant

MARKETING AUTHORISATION HOLDER: PHARMATEX ITALIA SRL - VIA APPIANI, 22 – 20121 MILAN ITALY
MANUFACTURER AND FINAL CONTROL RELEASER: FISIOPHARMA SRL - Nucleo Industriale - 84020 PALOMONTE (SA) - ITALY.

THERAPEUTIC INDICATIONS
Treatment and prophylaxis of venous and arterial thromboembolic disease.

CONTRAINDICATION
Heparin Sodium or Calcium must be avoided in patients with documented hypersensitivity to the drug or to some of the excipients;
- In patients with severe thrombocytopenia; in those in whom suitable blood coagulation tests e.g., the whole blood clotting time, and drawn partial thromboplastin time, cannot be performed at appropriate intervals (APTT). This contraindication refers to heparin anticoagulant dose. There is usually no need to monitor coagulation parameters in patients receiving prophylactic low-dose heparin (less than or equal to 0.2 ml 3 times a day for Heparin Calcium or 15000 units a day for Heparin Sodium);
- In patients with an uncontrollable active bleeding state: when it is associated with disseminated intravascular coagulation (DIC), the use of Heparin is to be evaluated in the specific clinical context;
- Local-regional anaesthesia for elective surgery procedures is contraindicated in patients who receive anticoagulant dose of Heparin;
- Haemorrhagic cerebrovascular accident;
- In the presence of organic lesions with high bleeding risk, the use of Heparin is to be evaluated in the specific clinical context considering the risk-benefit ratio in each single case;
- Only for Heparins containing benzyl alcohol: this product is contraindicated in new-born and until three years old children.

PRECAUTIONS FOR USE

Hemorrhage: Hemorrhage can occur at virtually any site in patients receiving heparin sodium and calcium. An unexplained fall in haematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a haemorrhagic event.

Heparin sodium or calcium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

- Cardiovascular: sub-acute bacterial endocarditis, severe hypertension not controlled by anti-hypertensive therapy;.
- Haematological: conditions associated with increased bleeding tendencies, such as haemophilia or coagulation factor defect, thrombocytopenia, thrombocytes disease and some vascular haemorrhagic purpuras (Rendu-Osler-like disease).
- Gastrointestinal: peptic ulcer, erosive oesuphagitis and gastritis, intestinal inflammatory disease in active phase, other gastro-enteric pathologies with haemorrhagic risk, continuous tube drainage of the stomach or small intestine.
- Surgical: during and immediately after (a) spinal tap or spinal anaesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.

Other: liver disease with alteration of coagulation parameters and/or oesophagus varices or gastric disease caused by portal hypertension with high haemorrhagic risk, miscarriage risk.

Coagulation Testing

When heparin sodium or calcium is administered in anticoagulant amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is over therapeutic interval or if hemorrhage occurs, dosage should be reduced or heparin should be discontinued promptly (see Uses and Administration).

Due to a transient action of heparin sodium, hemocoagulation tests turn to be within limits in a few hours; much longer times might be required in case of heparin calcium.

Thrombocytopenia caused by Heparin

It's a well known side effect which can occur 4 to 10 days after the beginning of the therapy, and even earlier in case of previous thrombocytopenia caused by Heparin. Mild thrombocytopenia (count greater than 100,000/mm^3) can occur in 10-20% of patients and may remain stable or reverse even if heparin is continued.

Otherwise in some cases (0.3 to 3% of cases), a more severe type may occur (thrombocytopenia type II), immune-mediated characterized by antibodies formation against heparin-platelet factor 4 complex. In these patients new thrombi associated with thrombocytopenia can develop, deriving by irreversible platelets aggregation induced by heparin, the so called "white thrombus syndrome". This process can cause severe thromboembolic consequences like skin necrosis, extremities gangrene which can lead to necessary amputation, myocardial infarction, pulmonary embolism, stroke and sometimes death. So, Heparin Sodium or calcium administration should be interrupted in case of both platelets defect and if a new thrombosis develops or a previous thrombosis gets worse in the patient. Continuation of anticoagulant therapy, for thrombosis which causes this treatment or for a new thrombus or a worsening, should be undertaken after heparin therapy suspension with an alternative anticoagulant. In these cases the use of low molecular weight heparins is dangerous because of the possibility of cross reaction, like an immediate starting of oral anticoagulant therapy (case of thrombosis worsening are described).

So any kind of thrombocytopenia must be carefully monitored. If platelet count falls below 100,000/mm^3 or if recurrent thrombosis develops the heparin sodium or calcium must be discontinued.

Platelet count should be monitored before therapy and then twice a week during the first month in case of prolonged administration.

Decreased sensitivity to Heparin

It can happen during fever, thrombosis, thrombophlebitis, infections with thrombotic tendency, inflammatory states, sometime during myocardial infarction, cancer, antithrombin III defect, and in post-surgical patients.
In case of heparin treatment with anticoagulant doses, avoid intramuscular drugs administration.
Only for medicines which contains chlorocresol
The presence of chlorocresol may cause hypersensitivity reactions.
In patients subjected to spinal or epidural anaesthesia, epidural analgesia or lumbar injection, prophylaxes with low doses of not fractionated heparin can rarely be associated with spinal or epidural haematomas which can cause prolonged or permanent paralysis. Risk is increased by the use of permanent epidural catheters for continuous perfusion, by concomitant administration of medicines which influences haemostasis like nonsteroidal anti-inflammatory drugs (FANS), platelet aggregation inhibitors or anticoagulant agents, by traumas or by repeated lumbar injections, by the presence of haemostasis disease or by old age. The presence of one or more of these risk factors must be carefully evaluated before this kind of anaesthesia/analgesia, during prophylaxes with unfractionated heparins.
Usually spinal catheters insertion must be performed after at least 8-12 hours from the last administration of unfractionated heparin (usually calcium heparin) at low prophylactic doses. Subsequent doses shouldn't be administered before 2-4 hours from the insertion or from removal of catheter, or should further on delayed or not administered in case of haemorrhagic expiration during initial positioning of spinal or epidural needle. Removal of permanent epidural catheter should be done at a time distance as maximum as possible (about 8-12 hours) from the last prophylactic dose of heparin given during anaesthesia.
If it is decided to administer unfractionated heparin before or after epidural or spinal anaesthesia, it must be paid extreme attention and performed a frequent monitoring in order to find signs and symptoms of neurological alterations like lumbar pain, sensorial and motor deficit (numbness and weakness of inferior limbs), bladder or intestinal function alterations. Nursing personnel should be instructed in order to characterize these signs and symptoms. Patients should be instructed to inform immediately medical or nursing personnel if one of the above symptoms appears.
If signs or symptoms of epidural or spinal haematomas signs or symptoms are suspected, an immediate diagnose must be performed and a treatment must be started which comprise spinal marrow decompression.

Use in pregnancy
Safety deriving from heparin use during pregnancy was not clearly proved.

INTERACTION WITH OTHER DRUGS
Oral anticoagulant
Heparin sodium or calcium at anticoagulant dose may lightly prolong the prothrombin time (increase of INR about 0.5). This aspect has to be considered in the evaluation of this parameter, above all when heparin and oral anticoagulant therapies are performed together. Close clinical-laboratory attention is recommended (frequent evaluation of PT and aPTT) in case of combined use of unfractionated heparin at anticoagulant doses with these medicines.
Platelet inhibitors
Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine or others that interfere with platelet-aggregation (the main haemostatic defence of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium or calcium, above all if it is at anticoagulant doses.
Other interactions
Digitalis, tetracyclines, nicotine, glucochorticoid, penicillins, phenotiazines, antihistamines may partially reduce the anticoagulant action of heparin.

SPECIAL PRECAUTIONS
Pharepa must be used under medical control.
The use of drug is safe in case of patients affected by celiac disease.
Keep out of the reach of children.

USES AND ADMINISTRATION

In accordance with medical prescription.

When heparin sodium or calcium is administered in anticoagulant amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is over therapeutic interval or if hemorrhage occurs, dosage should be reduced or heparin should be discontinued promptly (see Precaution for use).

Antagonist Protamine action

Protamine is useful for rapid neutralization of heparin activity, in case of great bleeding. Required quantity depends on administered heparin blood amount and on time elapsed from injection. Protamine administration must be performed by slow intravenous perfusion; 50 mg of Protamine neutralize 5000 I.U. of heparin.

Protamine dose which must be administered in order to neutralize heparin bolus decreases in proportion to elapsed time from bolus administration (immediately after bolus 100% of dose, after 1 hour 50%, after 2 hours 25%).

Protamine dose to be administered in case of continuous perfusion of heparin is the one useful to neutralize heparin I.U. perfused in the last 4 hours.

In case of treatment with subcutaneous heparin calcium at anticoagulant dose, a Protamine dose must be administered in order to neutralize about 25% of the last heparin dose, repeating this administration every three hours until 4 times.

OVER-DOSAGE

See paragraph Uses and Administration “Antagonist Protamine action”

ADVERSE REACTIONS

Hemorrhage

Hemorrhage is the chief complication that may result from heparin sodium or calcium treatment, particularly at anticoagulant doses. Coagulation times superior than therapeutic interval or small hemorrhages can be usually solved by reducing dosage or by suspending temporarily the therapy.

Bleeding

Gastro-enteric or urinary bleeding during anticoagulant therapy can reveal the presence of a hidden lesion reported below. Bleeding can occur in any area of the body but some specific haemorrhagic complications could be hard to be seen:

a) suprarenal hemorrhage, with subsequent acute suprarenal insufficiency was described during anticoagulant therapy. The treatment has to be interrupted if patient shows signs and symptoms of acute suprarenal insufficiency;
b) ovarian hemorrhage (corpus luteum) developed in fertile age women during a long or short term anticoagulant therapy;
c) retroperitoneal hemorrhages.

If hemorrhage is not miner, heparin therapy must be interrupted. In case of major hemorrhage, heparin already in the blood must be neutralized by introduction of Protamine (see paragraph “Antagonist Protamine action”).

Local reactions

Local irritation, erythema, mild pain, hematoma or ulceration may follow deep subcutaneous injection of heparin. These complications are much more common after intramuscular use, and such use is to be avoided, even occasionally.

Hypersensitivity

Generalised hypersensitivity reactions have been reported, with chills, fever, and urticaria, and rarely asthma, rhinitis, lacrimation, nausea and vomiting, and shock

Thrombocitopoenia

Thrombocytopenia has been reported to occur in patients receiving heparin sodium or calcium. (See Precaution for use).

Although it is mild and has no clinical significance, it can sometimes be accompanied by severe thrombotic and/or embolic complications.

After a long term administration of high doses of heparin, osteoporosis cases have been observed.
Skin necrosis, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipidemia have rarely been reported.
Rare cases of transaminase increase have also been reported.

Respect of instructions contained in the leaflet reduces adverse effect risk.

It is important that any adverse effect observed but not reported on the leaflet must be noted to the physician or pharmacist.

EXPIRY DATE AND STORAGE
Attention: do not use the product after expiry date reported on the box.

DATE OF LAST REVISION CARRIED OUT BY THE MINISTRY OF HEALTH: March 21, 2010