UNIHEPA 1000 IU/ ML INJECTION (5 ML VIAL)

DESCRIPTION:
UNIHEPA 1000 IU/ ML INJECTION (5 ML VIAL): A colourless or straw-coloured liquid, free from turbidity and from matter that deposits on standing.

COMPOSITION:
Each ml contains: Heparin Sodium BP (Bovine Mucosa) 1000 IU. Preservative: Benzyl Alcohol 1% w/v

PHARMACODYNAMICS:
Heparin is a naturally occurring mucopolysaccharide which inhibits the clotting of blood in vitro and in vivo. It enhances the rate at which antithrombin III neutralises thrombin and activated factor X (Xa). Antithrombin III also neutralises other activated coagulation factors, eg. factors IX, XI, XII and plasmin.
With low-dose heparin therapy, anticoagulation appears to result from neutralisation Xa which prevents the conversion of prothrombin to thrombin. With full-dose heparin therapy, anticoagulation appears to result primarily from neutralisation of thrombin which prevents the conversion of fibrinogen to fibrin. Full-dose heparin therapy also prevents the formation of a stable fibrin clot by inhibiting activation of fibrin stabilising factor.

PHARMACOKINETICS:
Heparin is not absorbed from the gastrointestinal tract and must be administered parenterally. Its onset of action is immediate following I.V. administration. There may be considerable variation among patients in the extent of absorption following deep subcutaneous injection of heparin; however, the onset of activity usually occurs within 20-60 minutes.
Heparin is extensively bound to plasma proteins. It does not cross the placenta and is not distributed into milk.
The metabolic fate of heparin is not fully understood. No biotransformation in plasma or liver, nor any renal excretory mechanism has been identified as primarily responsible for elimination of the drug. It has been suggested that transfer and storage in the reticuloendothelial system may play a role, or that heparin may be partially metabolised in the liver. After administration of large doses intravenously, a small fraction of unchanged drug is excreted in the urine.

INDICATIONS:
Heparin is indicated for prophylaxis and treatment of venous thrombosis and pulmonary embolism; in the treatment of myocardial infarction and arterial embolism; for prevention of clotting in arterial and heart surgery and for prevention of cerebral thrombosis. Heparin may also be used as an anticoagulant in blood transfusions, extra-corporal circulation, dialysis procedures, and for laboratory purposes

RECOMMENDED DOSAGE:

As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

Treatment Dosage:
Intravenous administration:
5,000 - 10,000 IU every 4 hours or 500 IU/kg bodyweight daily as a continuous infusion in sodium chloride injection or dextrose injection. Doses should be individually adjusted according to coagulation tests.
Subcutaneous administration:
The initial dose is 250 IU/kg bodyweight. Further doses should be given every 12 hours and individually adjusted according to coagulation tests.
Dosage adjustment:
It is recommended that dosages be adjusted to maintain a thrombin clotting time, whole blood clotting time or activated partial thromboplastin time 1.5 to 2 times that of control on blood withdrawn 4 - 6 hours after the first injection or commencement of infusion and at similar intervals until the patient is stabilised.
Prophylactic Dosage: Administration is by subcutaneous injection.
Patients undergoing major elective surgery: 5,000 IU should be given 2 hours pre-operatively and then every 8 - 12 hours post-operatively for 10 - 14 days or until the patient is ambulant, whichever is the longer.
Following myocardial infarction: 5,000 IU should be given twice daily for 10 days or until the patient is mobile.
Other patients: 5,000 IU should be given every 8 - 12 hours. These standard prophylactic regimens do not require routine control.
Dosage in Children:
Treatment Dosage:
Standard treatment dosages should be given initially. Subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.
Dosage in the Elderly:
Treatment Dosage:
Lower treatment dosages may be required. However, standard treatment dosages should be given initially and then subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.
Prophylactic Dosage:
Dosage alterations are unnecessary for prophylaxis in the elderly.
Pregnancy:
Treatment Dosage:
Standard treatment dosages should be given initially by continuous intravenous infusion, or every 12 hours by subcutaneous injection. Intermittent intravenous injections are not advised. Subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.
Prophylactic Dosage:
It is recommended that plasma heparin levels be maintained below 0.4 IU/ml as determined by specific anti-Xa assay. A suggested dosage is 5,000 IU every 12 hours in early pregnancy increasing to 10,000 IU every 12 hours in the last trimester. The dosage should be reduced during labour and the standard prophylactic dosage is suitable in the puerperium.

ROUTE OF ADMINISTRATION: For intermittent i.v. injection or i.v. infusion or deep s.c. injection.

CONTRAINDICATIONS:
Heparin therapy is contra-indicated in patients who are hypersensitive to the drug. It should not be used in the presence of actual or potential haemorrhagic states, eg. haemophilia, ascorbic acid deficiency or increased capillary fragility; threatened abortion; immediate postpartum period, subacute bacterial endocarditis; severe hypertension; gastric or duodenal ulcers; advanced renal or hepatic disease; during and immediately after spinal or major surgery, especially those involving the brain, eye or spinal cord.

WARNINGS AND PRECAUTIONS:
Heparin therapy should be given with caution to patients with impaired renal or hepatic function, or hypersensitivity to low molecular weight heparins.
Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.
In patients undergoing peridural or spinal anaesthesia or spinal puncture, the prophylactic use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. The risk is increased by the use of a peridural or spinal catheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants, and by traumatic or repeated puncture.
In decision making on the interval between the last administration of heparin at prophylactic doses and the placement or removal of a peridural or spinal catheter, the product characteristics and the patient

profile should be taken into account. Subsequent dose should not take place before at least four hours have elapsed.
Re-administration should be delayed until the surgical procedure is completed.
Should a physician decide to administer anti-coagulation in the context of peridural or spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment, such as back pain, sensory and motor deficits and bowel or bladder dysfunction. Patients should be instructed to inform immediately a nurse or a clinician if they experience any of these.
As there is a risk of antibody-mediated heparin-induced thrombocytopenia, platelet counts should be measured in patients receiving heparin treatment for longer than 5 days and the treatment should be stopped immediately in those who develop thrombocytopenia.

INTERACTIONS WITH OTHERS MEDICAMENTS:
Drugs which affect platelet function eg. aspirin and other non-steroidal anti-inflammatory agents, dextran and dipyridamole, may increase the risk of haemorrhage and should be used with caution in patients receiving heparin. Concomitant use of thrombolytic agents such as streptokinase or urokinase may also increase the risk of haemorrhage.
Heparin is incompatible with certain substances in aqueous solution. Reference to specialised literature should be made to verify in which solution the incompatibility was noted. The following incompatibilities have been reported: hydrocortisone; hyaluronidase; hydroxyzine; some antihistamines, narcotic analgesics, phenothiazines and antibiotics.

USE IN PREGNANCY AND LACTATION:
Use in Pregnancy: The use of heparin in pregnancy has the usual risks for the mother, in particular osteoporosis and thrombocytopenia. Although heparin does not cause malformations, an increased incidence of human foetal loss and prematurity associated with haemorrhage has been reported.
Use in Lactation: Heparin is not distributed into milk and heparin therapy is not therefore contra-indicated in women who are breast feeding.

SIDE EFFECTS:
Haemorrhage is the major risk of heparin therapy and may range from minor local ecchymoses to major haemorrhagic complications.
Delayed onset thrombocytopenia is also a possible complication of heparin therapy. If this occurs, the drug should be withdrawn immediately.
Skin necrosis has infrequently been reported at injection sites. It is thought to be a localised manifestation of heparin induced platelet aggregation and thrombosis and should be taken as a warning sign in patients who develop it. Heparin should be discontinued immediately.
Allergic reactions to heparin occur rarely. Hypersensitivity may be manifested by pruritus, urticaria, asthma-like symptoms and anaphylactoid reactions.
Osteoporosis complicated by spontaneous bone fracture has been reported with prolonged use of large doses of heparin. Transient alopecia and diarrhea may occur.
Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium.

SYMPTOMS AND TREATMENT OF OVERDOSE:
Slight haemorrhage due to overdosage can usually be treated by withdrawing the drug. Severe bleeding may be reduced by the administration of protamine sulphate. Protamine sulphate should be administered intravenously. To avoid circulatory side effects, the injection should be given slowly at a rate of 5 mL over a period of about 10 minutes. Not more than 50 mg should be given at any one time. The dose of protamine sulphate required is governed by the amount of heparin that has to be neutralised; approximately 1 mg of protamine sulphate neutralises 110 units of heparin (mucous) that has been injected in the previous 15 minutes. Since heparin is being continuously excreted, the dose should be reduced as more time elapses after the heparin injection. Ideally, the dose of protamine sulphate required should be accurately determined by titration methods as the antagonist itself, in gross excess, acts as an anticoagulant.

INCOMPATIBILITIES:
Incompatibility has been reported between heparin (sodium and calcium) and amikacin sulphate, amiodarone, ampicillin sodium, benzylpenicillin sodium, cephalothin sodium, ciprofloxacin lactate, daunorubicin hydrochloride, dobutamine hydrochloride, doxorubicin hydrochloride, erythromycin lactobionate, gentamicin sulphate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulphate, methicillin sodium, opioid analgesics, oxytetracycline hydrochloride, polymyxin B sulphate, promazine hydrochloride, promethazine hydrochloride, streptomycin sulphate, sulphafurazole diethanolamine, tetracycline hydrochloride, tobramycin sulphate and vancomycin hydrochloride. Admixture with glucose can have variable effects. Heparin is strongly acidic and is incompatible with many solutions containing medications, although no loss of activity occurs when the agents are given via separate administration sites. Also, heparin may be incompatible with solutions containing a phosphate buffer, sodium carbonate, or sodium oxalate. It is recommended that heparin not be mixed, or administered through the same intravenous line, with other medications unless compatibility has first been established. In addition, heparin may be inactivated when used in conjunction with an artificial kidney because of an influx of calcium, magnesium, and acetate ions from the dialysate.

STORAGE CONDITIONS:
Store below 30˚C. Protect from light & freezing.
When diluted with 0.9% sodium chloride or 5% dextrose should be used within 24 hours if stored in 2-8°C or used within 4 hours if stored in 25°C.
KEEP OUT OF REACH OF CHILDREN. JAUHKAN DARIPADA KANAK-KANAK.

PACK SIZES:
Pack in 10's vials of 5 ml / box.

SHELF LIFE:
Please refer to outer package.

PRODUCT REGISTRATION HOLDER AND MANUFACTURER:
DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59, Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA

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