For the use of Registered Medical Practitioner of Hospital or a Laboratory only

Heparin Injection BP 5000IU/ml

COMPOSITION

Each ml contains

Heparin Sodium	BP	5000IU
(Source: Porcine intestinal mucosa)		
Benzyl Alcohol	BP	0.9%w/v
(As preservative)		
Water for Injection	BP	q.s

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents

ATC code: B01AB01

Heparin prevents the coagulation of blood in-vivo and in-vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X.

Pharmacokinetic properties

Absorption

Heparin is not absorbed from the gastrointestinal tract. Heparin is administered by injection.

Distribution

Heparin binds extensively to plasma proteins.

Metabolism

Heparin does not undergo enzymatic degradation.

Elimination

Heparin and its metabolites are excreted in the urine.

The half-life of heparin depends on the dose administered, the route of administration and is subject to wide inter- and intra-individual variation.

INDICATION AND USAGE

- Prophylaxis of deep vein thrombosis and pulmonary embolism.
- Treatment of deep vein thrombosis and pulmonary embolism, unstable angina pectoris and acute peripheral arterial occlusion.
- Prophylaxis of mural thrombosis following myocardial infarction.
- In extracorporeal circulation and haemodialysis.

CONTRA-INDICATION

Hypersensitivity to the active substance, sodium metabisulphite or any of the excipients.This heparin formulation contains the preservative benzyl alcohol and so must not be given to children up to 3yrs old or neonates. As benzyl alcohol may cross the placenta the use of this formulation must be avoided in pregnancy.

Current (or history of) heparin-induced thrombocytopenia. Generalised or local haemorrhagic tendency.

An epidural anaesthesia during birth in pregnant women treated with heparin is contraindicated.

Regional anaesthesia in elective surgical procedures is contra-indicated because the use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis.

DRUG INTERACTIONS

Heparin may prolong the one stage prothrombin time. Accordingly, when Heparin is given with dicoumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose of heparin should elapse before blood is drawn, if a valid prothrombin time is to be obtained.

The anticoagulant effect of heparin may be enhanced by concomitant medication with other drugs affecting platelet function or the coagulation system, e.g. platelet aggregation inhibitors, thrombolytic agents, salicylates, non-steroidal anti-inflammatory drugs, vitamin K antagonists, dextrans, activated protein C. Where such combination cannot be avoided, careful clinical and biological monitoring is required.

Combined use with ACE inhibitors or angiotensin II antagonists may increase the risk of hyperkalaemia.

Nitrates: Reduced activity of heparin has been reported with simultaneous intravenous glyceryl trinitrate infusion.

WARNINGS AND PRECAUTIONS

Warnings

Heparin should be used with caution in patients with hypersensitivity to low molecular weight heparin.

Care should be taken when heparin is administered to patients with increased risk of bleeding complications, hypertension, renal or hepatic insufficiency.

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.

Drugs affecting platelet function or the coagulation system should in general not be given concomitantly with heparin.

In patients undergoing peri-dural 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 peri-dural or spinal catheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs, 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 peri-dural 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.

Heparin should not be administered by intramuscular injection due to the risk of haematoma.

Due to increased bleeding risk, care should be taken when giving concomitant intramuscular injections, lumbar puncture and similar procedures.

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.

Heparin induced thrombocytopenia and heparin induced thrombocytopenia with thrombosis can occur up to several weeks after discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for heparin induced thrombocytopenia and heparin induced thrombocytopenia with thrombosis.

This medicinal product contains 23.5 mg sodium per 5 ml ampoule, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Heparin Injection contains benzyl alcohol (10mg/ml) as preservatives. Caution should be used if prescribing Heparin Injection to susceptible patients. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to three years old.

SIDE EFFECTS

The following adverse reactions have been observed and reported during treatment with Heparin Sodium with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (<1/10 000), not known (cannot be estimated from available data).

Adverse Drug Reactions

System Organ Class (SOC)	MedDRA Preferred Term	Frequency
Vascular disorders	Haemorrhage	Not known
	Epistaxis	Not known
	Contusion	Not known
Blood and lymphatic system disorders	Thrombocytopenia	Not known
Renal and urinary disorders	Haematuria	Not known
Endocrine disorders	Adrenal insufficiency	Not known
	Hypoaldosteronism	Not known
Skin and subcutaneous tissue disorders	Alopecia	Not known
	Skin necrosis	Not known
Musculoskeletal, connective tissue and bone disorders	Osteoporosis	Not known
Immune system disorders	Hypersensitivity	Not known
Metabolism and nutrition disorders	Rebound hyperlipidaemia	Not known
	Hyperkalaemia Hypokalaemia	Not known
Reproductive system and breast disorders	Priapism	Not known
General disorders and administration site conditions	Injection site reaction	Not known
Investigations	Alanine aminotransferase increased; Aspartate aminotransferase increased	Not known

Erythematous nodules, or infiltrated and sometimes eczema-like plaques, at the site of subcutaneous injections are common, occurring 3-21 days after starting heparin treatment.

Haemorrhage:

Haemorrhage is the chief complication that may result from heparin therapy. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug. It should be appreciated that gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site but certain specific haemorrhage complications may be difficult to detect.

Adrenal haemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal haemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None stated.

OVERDOSE

Bleeding is the main sign of overdose with heparin.

As heparin is eliminated quickly, a discontinuation of treatment is sufficient in case of minor haemorrhages. In case of severe haemorrhages heparin may be neutralised with protamine sulphate injected slowly intravenously. One mg of protamine sulphate neutralises approximately 100 IU of heparin. Nevertheless, the required protamine sulphate dose varies according to the time of heparin administration and the dose administered.

It is important to avoid overdosage of protamine sulphate because protamine itself has anticoagulant properties. A single dose of protamine sulphate should never exceed 50 mg. Intravenous injection of protamine may cause a sudden fall in blood pressure, bradycardia, dyspnoea and transitory flushing, but these may be avoided or diminished by slow and careful administration.

DOSAGE & MODE OF ADMINISTRATION

Posology:

Prophylaxis of deep vein thrombosis and pulmonary embolism

Adults:

2 hours pre-operatively:	5,000 units subcutaneously
followed by:	5,000 units subcutaneously every 8-12 hours, for 7-10 days or until the patient is fully ambulant.

No laboratory monitoring should be necessary during low dose heparin prophylaxis. If monitoring is considered desirable, anti-Xa assays should be used as the activated partial thromboplastin time (APTT) is not significantly prolonged.

Elderly:

Dosage reduction and monitoring of APTT may be advisable.

Paediatric population: No dosage recommendations.

Treatment of deep vein thrombosis and pulmonary embolism:

Adults:

Loading dose: 5,000 units intravenously (10,000 units may be required in severe pulmonary embolism)

Maintenance: 1,000-2,000 units/hour by intravenous infusion, or 10,000-20,000 units 12 hourly subcutaneously, or 5,000-10,000 units 4-hourly by intravenous injection.

Elderly:

Dosage reduction may be advisable.

Children and small adults:

Loading dose: 50 units/kg intravenously

Maintenance: 15-25 units/kg/hour by intravenous infusion, or 250 units/kg 12 hourly subcutaneously, or 100 units/kg 4-hourly by intravenous injection.

Treatment of unstable angina pectoris and acute peripheral arterial occlusion:

Adults:

Loading dose: 5,000 units intravenously

Maintenance: 1,000-2,000 units/hour by intravenous infusion, or 5,000-10,000 units 4-hourly by intravenous injection.

Elderly:

Dosage reduction may be advisable.

Children and small adults:

Loading dose: 50 units/kg intravenously

Maintenance: 15-25 units/kg/hour by intravenous infusion, or 100 units/kg 4-hourly by intravenous injection.

Daily laboratory monitoring (ideally at the same time each day, starting 4-6 hours after initiation of treatment) is essential during full-dose heparin treatment, with adjustment of dosage to maintain an APTT value 1.5-2.5 x midpoint of normal range or control value.

Prophylaxis of mural thrombosis following myocardial infarction

Adults:

12,500 units 12 hourly subcutaneously for at least 10 days.

Elderly:

Dosage reduction may be advisable

In extracorporeal circulation and haemodialysis

Adults:

Cardiopulmonary bypass:

Initially 300 units/kg intravenously, adjusted thereafter to maintain the activated clotting time (ACT) in the range 400-500 seconds.

Haemodialysis and haemofiltration: Initially 1,000-5,000 units,

Maintenance: 1,000-2,000 units/hour, adjusted to maintain clotting time >40 minutes.

Heparin resistance

Patients with altered heparin responsiveness or heparin resistance may require disproportionately higher doses of heparin to achieve the desired effect. Also refer to section 4.4, Special warnings and precautions for use.

Method of administration

By continuous intravenous infusion in 5% glucose or 0.9% sodium chloride or by intermittent intravenous injection, or by subcutaneous injection.

The intravenous injection volume of heparin injection should not exceed 15ml. As the effects of heparin are short-lived, administration by intravenous infusion or subcutaneous injection is preferable to intermittent intravenous injections.

PREGNANCY AND LACTATION

Pregnancy

There was evidence of maternal toxicity and embryofetal toxicity in animal studies .

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal blood concentrations.

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

Clindamycin should be used in pregnancy only if clearly needed.

Breast-feeding

Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from 0.7 to 3.8 µg/mL. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.

Fertility

Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability.

STORAGE CONDITION

Store at 20° to 25°C. Don't allow to freeze

KEEP OUT OF REACH OF CHILDREN

PRESENTATION

5ml Vial packed in cardboard carton along with pack insert.

Pack of 5 Vials.

MANUFACTURED IN INDIA

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