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

Heparin Sodium Injection IP 5000 IU / 25000 IU

ADHESTOP 5000 IU

Each ml contains:

Heparin Sodium IP (Derived from Intestinal Porcine Mucosa)	1000 IU
Benzyl Alcohol IP (Preservative)	0.95% w/v
Water for Injections IP	q.s.

ADHESTOP 25000 IU

Each ml contains:

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Benzyl Alcohol IP (Preservative)	0.95% w/v
Water for Injections IP	q.s.

DESCRIPTION:

Heparin Sodium is the sodium salt of sulphated glycosaminoglycans present as a. mixture of heterogeneous molecules varying in molecular weights. It is composed of polymers of alternating derivatives of D-glucosamine (N-sulphated, O-sulphated, or N-acetylated) and uronic acid, L-iduronic acid or D-glucuronic acid) joined by glycosidic linkages. It is a white or greyish-white powder; moderately hygroscopic.

THERAPEUTIC INDICATIONS:

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

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Prophylaxis of deep vein thrombosis and pulmonary embolism
Adults:
2 hours pre-operatively: 5,000 IU subcutaneously
followed by: 5,000 IU 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, 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 5,000-10,000 units 4-hourly by intravenous injection.
Elderly:
Dosage reduction may be advisable.
Children and adolescents:
Loading dose: 50 units/kg intravenously
Maintenance: 15-25 units/kg/hour by intravenous infusion, or 100 units/kg 4-hourly by intravenous injection

Treatment of unstable angina pectoris and acute peripheral arterial occlusion

Adults:
Loading dose: 5,000 IU intravenously
Maintenance: 1,000-2,000 IU/hour by intravenous infusion, or 5,000-10,000 IU 4-hourly by intravenous injection
Elderly:
Dosage reduction may be advisable.
Children and small adults:
Loading dose: 50 IU/kg intravenously
Maintenance: 15-25 IU/kg/hour by intravenous infusion, or 100 IU/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 IU 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. (See section Special warnings and precautions for use).

Method of administration

By continuous intravenous infusion or by intermittent intravenous injection or by subcutaneous injection. The intravenous injection volume of heparin injection should not exceed 15 mL. As the effects of heparin are short-lived, administration by intravenous infusion or subcutaneous injection is preferable to intermittent intravenous injections.
Only use if the solution is clear and colourless, and free of visible particles. Any unused medicinal product or waste materials should be disposed of in accordance with local requirements.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients being used in formulation.
After major trauma, during surgery of the brain, spinal cord and eye, in procedures at sites where there is a risk of bleeding, in patients that have had recent surgery, and in patients undergoing lumbar puncture or regional anaesthetic block.
Patients who consume large amounts of alcohol, who have generalised or local haemorrhagic tendency, who are actively bleeding, have haemophilia or other bleeding disorders, including severe liver disease (including oesophageal varices), purpura, severe hypertension, active tuberculosis or increased capillary permeability.
Patients with present or previous thrombocytopenia. The rare occurrence of skin necrosis in patients receiving heparin contraindicates the further use of heparin either by subcutaneous or intravenous routes because of the risk of thrombocytopenia.
The relative risks and benefits of heparin should be carefully assessed in patients with a bleeding tendency or those patients with an actual or potential bleeding site eg. hiatus hernia, peptic ulcer, neoplasm, bacterial endocarditis, retinopathy, bleeding haemorrhoids, suspected intracranial haemorrhage, cerebral thrombosis or threatened abortion.
In patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedures is contraindicated because use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. If such a procedure is planned the heparin should be stopped and the procedure should be delayed until the aPTT has returned to normal. Epidural anaesthesia use during birth in pregnant women treated with heparin is contraindicated (See section Fertility, pregnancy and lactation)
Threatened abortion. Menstruation is not a contra-indication. Concomitant use of intravenous diclofenac (including low dose heparin) is contraindicated.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

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 (HIT) and heparin induced thrombocytopenia with thrombosis (HITT) 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 HIT or HIT. In patients with advanced renal or hepatic disease, a reduction in dosage may be necessary. The risk of bleeding is increased with severe renal impairment and in the elderly (particularly elderly women).
Although heparin hypersensitivity is rare, it is advisable to give a trial dose of 1,000 I.U. in patients with a history of allergy. Caution should be exercised in patients with known hypersensitivity to low molecular weight heparins.
In most patients, the recommended low-dose regimen produces no alteration in clotting time. However, patients show an individual response to heparin, and it is therefore essential that the effect of therapy on coagulation time should be monitored in patients undergoing major surgery.
Caution is recommended in patients receiving heparin prophylactically and undergoing spinal or epidural anaesthesia or spinal puncture (risk of spinal or epidural 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. Readministration should be delayed until the surgical procedure is completed.
In patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedures is contraindicated because the use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. If such a procedure is planned the heparin should be stopped and the procedure should be delayed until the aPTT has returned to normal.
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 can suppress adrenal secretion of aldosterone leading to hyperkalemia, 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 hyperkalemia 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 in all patients treated for more than 7 days.
Due to increased bleeding risk, care should be taken when giving concomitant intramuscular injections, lumbar puncture and similar procedures.
Heparin resistance
There is considerable variation in individual anticoagulant responses to heparin.
Heparin resistance, defined as an inadequate response to heparin at a standard dose for achieving a therapeutic goal occurs in approximately 5 to 30% of patients.
Factors predisposing to the development of heparin resistance, include:

- Antithrombin III activity less than 60% of normal (antithrombin III-dependent heparin resistance):

Reduced antithrombin III activity may be hereditary or more commonly, acquired (secondary to preoperative heparin therapy in the main, chronic liver disease, nephrotic syndrome, cardiopulmonary bypass, low grade disseminated intravascular coagulation or drug induced, e.g. by aprotinin, oestrogen or possibly nitroglycerin)

- Patients with normal or supranormal antithrombin III levels (antithrombin III-independent heparin resistance)
  - Thromboembolic disorders
  - Increased heparin clearance
- Elevated levels of heparin binding proteins, factor VIII, von Willebrand factor, fibrinogen, platelet factor 4 or histidine-rich glycoprotein
  - Active infection (sepsis or endocarditis)
  - Preoperative intra-aortic balloon counterpulsation
  - Thrombocytopenia
  - Thrombocytosis
  - Advanced age
  - Plasma albumin concentration ≤ 35g/dl
  - Relative hypovolaemia

Heparin resistance is also often encountered in acutely ill patients, in patients with malignancy and during pregnancy or the post-partum period.
Drugs affecting platelet function or the coagulation system should in general not be given concomitantly with heparin. (See section Interaction with other medicinal products and other forms of interaction).
This medicinal product contains 82.52 mg sodium per ampoule of 20ml, equivalent to 4% of the WHO recommended maximum daily intake of 2g sodium for an adult.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
Analgesics:
Drugs that interfere with platelet aggregation eg. aspirin and other NSAIDs should be used with care. Increased risk of haemorrhage with ketorolac or intravenous diclofenac (avoid concomitant use even with low-dose heparin).
Anticoagulants, platelet inhibitors, etc:
Increased risk of bleeding with oral anticoagulants, epoprostenol, clopidogrel, ticlopidine, streptokinase, dipyridamole, dextran solutions or any other drug which may interfere with coagulation.
Cephalosporins:
Some cephalosporins, e.g. cefaclor, cefixime and ceftriaxone, can affect the coagulation process and may therefore increase the risk of haemorrhage when used concurrently with heparin.
ACE inhibitors, angiotensin-II receptor antagonists or the renin inhibitor:
Hyperkalaemia may occur with concomitant use.
Nitrates:
Reduced activity of heparin has been reported with simultaneous intravenous glyceryl trinitrate infusion.
Probenecid:
May increase the anticoagulant effects of heparin.
Tobacco smoke:
Nicotine may partially counteract the anticoagulant effect of heparin. Increased heparin dosage may be required in smokers.
0Interference with diagnostic tests may be associated with pseudo-hypocalcaemia (in haemodialysis patients), artefactual increases in total thyroxine and triiodothyronine, simulated metabolic acidosis and inhibition of the chromogenic lysate assay for endotoxin. Heparin may interfere with the determination of aminoglycosides by immunoassays.

FERTILITY, PREGNANCY AND LACTATION:
Pregnancy
Heparin is not contraindicated in pregnancy. Heparin does not cross the placenta or appear in breast milk. The decision to use heparin in pregnancy should be taken after evaluation of the risk/benefit in any particular circumstances.
Osteoporosis has been reported with prolonged heparin treatment during pregnancy.
Particular caution is required at the time of delivery. Due to the risk of uteroplacental hemorrhage, heparin treatment should be stopped at the onset of labor.
Epidural anesthesia uses during birth in pregnant women treated with heparin is contraindicated. If epidural anesthesia is envisaged, heparin treatment should be suspended whenever possible.
Use in women with threatened abortion is contraindicated. (See section Contraindications).
Lactation
Heparin does not cross the placenta or appear in breast milk.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Heparin has no or negligible influence on the ability to drive or use machines.

UNDESIRABLE EFFECTS
Blood and lymphatic system disorder
Haemorrhage(See section Special warnings and precautions for use and overdose).
Thrombocytopenia has been observed occasionally (see section Special warnings and precautions for use). It has been reported that thrombocytopenia occurs more frequently with bovine-derived heparin than porcine-derived heparin. Two types of heparin-induced thrombocytopenia have been defined. Type I is frequent, mild (usually >50 x 109/L) and transient, occurring within 1-5 days of heparin administration. Type II is less frequent but often associated with severe thrombocytopenia (usually>50 x 109/L) and transient, occurring within 1-5 days of heparin administration. Type II is less frequent but often associated with severe thrombocytopenia (usually <50 x 109/L) It is immune-mediated and occurs after a week or more (earlier in patients previously exposed to heparin). It is associated with the production of a platelet-aggregating antibody and thromboembolic complications, due to platelet-rich thrombi (the 'white clot syndrome'), which may precede the onset of thrombocytopenia. Pulmonary embolism has been reported as thromboembolic complications of heparin-induced thrombocytopenia. Heparin should be discontinued immediately in patients who develop thrombocytopenia.
Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT) can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT and HITT.
Immune system disorders
Hypersensitivity reactions to heparin are rare They include urticaria, conjunctivitis, rhinitis, asthma, cyanosis, tachypnoea, feeling of oppression, fever, chills, angioneurotic oedema and anaphylactic shock.
Metabolism and nutrition disorders
Heparin administration is associated with release of lipoprotein lipase into the plasma; rebound hyperlipidaemia may follow heparin withdrawal.
Vascular disorders
Haematoma. Very rare cases of epidural and spinal haematoma have been reported in patients receiving heparin for prophylaxis undergoing spinal or epidural anesthesia or spinal puncture.
Hepatobiliary disorders
Increased serum transaminase values may occur but usually resolve on discontinuation of heparin.
Endocrine disorders
Adrenal insufficiency secondary to adrenal haemorrhage has been associated with heparin (rarely). Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalemia may occur particularly in patients with chronic renal failure and diabetes mellitus
Skin and subcutaneous tissue disorder
Local irritation and skin necrosis may occur but are rare. If this occurs treatment must be withdrawn immediately.
Alopecia: there is some evidence that prolonged dosing with heparin (i.e. over many months) may cause alopecia.
Pruritus
Rash (including erythematous and maculopapular)
Musculoskeletal and connective tissue disorders
There is some evidence that prolonged dosing with heparin (i.e. over many months) may cause osteoporosis and fractures in the vertebra and ribs. Significant bone demineralization has been reported in women taking more than 10,000 I.U. per day of heparin for three months or longer.
Reproductive system and breast disorders
Priapism has been reported.

OVERDOSE:
A potential hazard of heparin therapy is hemorrhage, but this is usually due to overdosage and the risk is minimized by strict laboratory control. Slight hemorrhage can usually be treated by withdrawing the drug. If bleeding is more severe, clotting time and platelet count should be determined. Prolonged clotting time will indicate the presence of an excessive anticoagulant effect requiring neutralization by intravenous protamine sulfate, at a dosage of 1 mg for every 100 I.U. of heparin to be neutralized. The bolus dose of protamine sulfate should be given slowly over about 10 minutes and not exceed 50 mg. If more than 15 minutes have elapsed since the injection of heparin, lower doses of protamine will be necessary.

PHARMACOLOGICAL PROPERTIES:
Pharmacotherapeutic group: Antithrombotic agents
ATC code: B01AB01
Pharmacodynamic properties:
Heparin is a naturally occurring anticoagulant which 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.
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.

STORAGE: Store at temperature not exceeding 30ºC.

PRESENTATION:
ADHESTOP 5000 IU/ ADHESTOP 25000 IU
Primary Packing: 7.5 ml clear glass vial USP Type I.
Secondary Packing: Such 25 vials packed in monocaton along with package insert.

Mfd. by:
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