

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Heparin Sodium BP 2500 IU/L in 0.9% w/v Sodium Chloride IV Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin Sodium BP	2500 IU/L
Sodium Chloride EP	9.0 g/L
Disodium Phosphate Dodecahydrate EP	5.8 g/L
Citric Acid Monohydrate EP	405 mg/L

3 PHARMACEUTICAL FORM

Sterile non pyrogenic aqueous solution intended for intravenous administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Heparin sodium in 0.9% Sodium Chloride infusion is indicated as an anticoagulant in extra corporeal circulation and dialysis procedures, and as an aid in the maintenance of catheter patency.

4.2 Posology and method of administration

Dosage

Dosage of heparin should be titrated against patient response.

Heparinisation for dialysis procedures

Dosage is dependent upon the age, weight and clinical condition of the patient. It is suggested that a proper heparinisation schedule is used before, and maintained throughout the procedure to prevent clotting and subsequent blood path obstruction.

Maintenance of Catheter Patency

The dosage should be adapted to catheter characteristics and the clinical condition of the patient.

Administration

Administration is by intravenous infusion.

Elderly patients

A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Clinical studies indicate that lower doses of heparin may be indicated in these patients.

4.3 Contraindications

Heparin sodium should not be used in patients:

- with a history of hypersensitivity to heparin
- with severe thrombocytopenia
- with an uncontrollable active bleeding state such as haemophilia, except when this is due to disseminated intravascular coagulation

4.4 Special warnings and precautions for use

The intravenous administration of solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injections. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the injections.

Excessive administration of potassium free solutions may result in significant hyperkalaemia.

Heparin Sodium BP in 0.9% Sodium Chloride intravenous infusion must be used with caution in patients who have impaired ability to handle sodium, such as renal insufficiency and congestive heart failure, and in clinical states in which there exists oedema with sodium retention..

Do not use unless solution is clear and container undamaged. Heparin sodium BP in 0.9% w/v sodium chloride intravenous infusion should not be administered orally.

Heparin should be used with extreme care in patients suffering from conditions in which there is an increased danger of haemorrhage. Haemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in haematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of haemorrhagic event.

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

Cardiovascular - Subacute bacterial endocarditis. Severe hypertension.

Surgical - During and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.

Haematologic - Conditions associated with increased bleeding tendencies, such as haemophilia, thrombocytopenia, and some vascular purpuras.

Gastrointestinal - Ulcerative lesions and continuous tube drainage of the stomach or small intestine.

Other - Menstruation, liver disease with impaired haemostasis.

Periodic hematocrit tests, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

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 in all patients treated for more than 7 days.

Thrombocytopenia is commonly seen in patients receiving heparin. Platelet counts should be obtained at baseline and periodically during heparin administration. Mild thrombocytopenia (count greater than $100,000/\text{mm}^3$) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below $100,000/\text{mm}^3$ or if recurrent thrombosis develops, the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

HIT is a serious immune-mediated disorder resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as HIT with thrombosis. Thrombotic events may also be the initial presentation for HIT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis,

skin necrosis, gangrene of the extremities that may lead to amputation, and fatal outcomes.

Once HIT (with or without thrombosis) is diagnosed or strongly suspected, heparin sodium (including heparin flushes) should be discontinued and an alternative anticoagulant used. Future use of heparin sodium, especially within 3 to 6 months following the diagnosis of HIT (with or without thrombosis), and while patients test positive for HIT antibodies, should be avoided.

Elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have been commonly seen in patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.

Resistance to heparin has been noted in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

These solutions should be used with caution in patients receiving corticosteroids or corticotropin.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others which interfere with platelet aggregation (the main haemostatic defense of heparinised patients) may induce bleeding and should be used with caution in patients on heparin therapy.

The use of ACE inhibitors and angiotensin-II antagonists in conjunction with heparin increase the risk of hyperkalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of heparin sodium in 0.9% w/v Sodium Chloride intravenous infusion has not been demonstrated in pregnant women.

There are no or limited amount of data from the use of Heparin Sodium in pregnant women. Animal studies are insufficient with respect to reproductive toxicity.

Heparin Sodium is not recommended during pregnancy.

Breast-feeding:

Heparin does not pass the placental barrier; it is not excreted in human milk Heparin Sodium can be used during breast-feeding.

4.7. Effects on Ability to Drive and Use Machines

Not applicable.

4.8 Undesirable effects

The most frequently reported undesirable effects are bleeding events, reversible increase in liver enzymes, thrombocytopenia and various skin reactions. Allergic reactions, skin necrosis and priapism have also been reported.

The following adverse reactions have been observed and reported during treatment with Heparin Sodium with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ 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
	Hypoadosteronism	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 hyperlipemia	Not known
	Hyperkalaemia	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

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.

Ovarian (corpus luteum) haemorrhage developed in a number of women of reproductive age receiving short or long-term anticoagulant therapy. This complication if unrecognized may be fatal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Bleeding is the chief sign of heparin overdose.

Protamine Sulphate (1% w/v solution) by slow intravenous infusion will neutralise heparin. No more than 50 mg should be given very slowly in any 10 minute period. Each mg of protamine sulphate neutralises approximately 100 units of heparin (or 1.0 to 1.5 mg neutralises approximately 1.0 mg of heparin). Heparins derived from various animal sources require different amounts of protamine sulphate for neutralisation.

Decreasing amounts of protamine are required as time from the last heparin injection increases. Thirty minutes after a dose of heparin, approximately 0.5 mg of protamine is sufficient to neutralise each 100 units of heparin. Blood or plasma transfusions may be necessary; these dilute but do not neutralise heparin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Heparin inhibits reactions which lead to the clotting of blood and the formulation of fibrin clots in vivo and in vitro. Heparin does not have fibrinolytic activity and thus will not lyse existing clots. It will however rapidly prevent thrombus formation and limit the release of vaso active substances from platelets adhering to the thrombi.

Heparin exerts an anticoagulant effect by catalytically accelerating the binding and inactivation by antithrombin III of thrombin and other activated clotting factors

5.2. Pharmacokinetic Properties

None presented.

5.3 Preclinical safety data

No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis

Animal reproduction studies have not been conducted with heparin sodium.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injection EP to 1000ml

6.2. Incompatibilities

Do not add other drugs to Heparin Sodium in 0.9% Sodium Chloride Intravenous Infusion.

6.3 Shelf life

The shelf life is 15 months providing the unit has not been opened.

6.4. Special Precautions for Storage

Storage temperature should not exceed 25°C.

6.5. Nature and Contents of Container

PVC Viaflex[®] containers of either 500ml or 1000ml volume enclosed within a plastic overpouch.

6.6. Instructions for Use/Handling

Do not use unless solution is clear and the container is undamaged.

Discard any unused portion.

Do not reconnect partially used bags.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 0116/0131

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/07/2007

10 DATE OF REVISION OF THE TEXT

11/11/2014