

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Heparin Sodium BP 1000 IU/l in 0.9% w/v Sodium Chloride IV Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin Sodium	1000 IU/l
Sodium Chloride	9.0g/l
Disodium Phosphate dodecahydrate	5.8g/l
Citric Acid Monohydrate	405mg/l

This provides: 186 mmol/l Sodium, 154 mmol/l Chloride, 16 mmol/l Phosphate and 2 mmol/l Citrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion (Infusion)
Clear, colourless or straw coloured, sterile non-pyrogenic solution for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Heparin sodium in 0.9% Sodium Chloride infusion is indicated as an anticoagulant in extracorporeal circulation and dialysis procedures for 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

- 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
- with jaundice, threatened abortion, bacterial endocarditis, peptic or hiatal ulceration, retinopathy or in those with evidence of, or a potential for, bleeding (e.g. subdural haematoma).

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 hypokalemia.

In patients with diminished renal function, administration may result in sodium retention.

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.

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

Heparin sodium 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 - 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.

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

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

Other - Menstruation, liver disease with impaired hemostasis.

Heparin should only be used with great caution in patients with severe hypertension, during and immediately following spinal tap or spinal anesthesia major surgery, especially involving the brain, spinal cord, or eye, conditions associated with increased bleeding tendencies, such as thrombocytopenia, and some vascular purpuras, ulcerative lesions and continuous tube drainage of the stomach or small intestine, menstruation and liver disease with impaired haemostasis

Heparin should only be used with great caution in patients with severe liver or kidney dysfunction, recently active cerebrovascular disease, or in those who have undergone recent surgery or trauma.

Heparin should only be administered in Units in which regular monitoring of coagulation time can be carried out. Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

Drugs which interfere with platelet aggregation may induce bleeding and should be used with caution in patients on heparin therapy.

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 has been reported to occur in patients receiving heparin with a reported incidence of up to 30%. Platelet counts should be obtained at baseline and periodically during heparin administration. Clinically important thrombocytopenia is immune-mediated and does not usually develop until 6 to 10 days following treatment; it may be complicated by thrombosis. Mild thrombocytopenia (count greater than 100,000/mm³) 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/mm³ or if recurrent thrombosis develops the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis)

HIT is a serious immune-mediated reaction 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, all heparin sodium sources (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.

Immune-mediated HIT is diagnosed based on clinical findings supplemented by laboratory tests confirming the presence of antibodies to heparin sodium, or platelet activation induced by heparin sodium. A drop in platelet count greater than 50% from baseline is considered indicative of HIT. Platelet counts begin to fall 5 to 10 days after exposure to heparin sodium in heparin sodium-naïve individuals, and reach a threshold by days 7 to 14. In contrast, “rapid onset” HIT can occur very quickly (within 24 hours following heparin sodium initiation), especially in patients with a recent exposure to heparin sodium (i.e. previous 3 months). Thrombosis development shortly after documenting thrombocytopenia is a characteristic finding in almost half of all patients with HIT.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³ or if recurrent thrombosis develops, the heparin product should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Delayed Onset of HIT (With or Without Thrombosis)

Heparin-induced thrombocytopenia (with or without thrombosis) can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin sodium should be evaluated for HIT (with or without thrombosis).

Heparin Resistance

Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

Increased Risk in Older Patients, Especially Women

A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

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 aspirin, dextran solutions, phenylbutazone, ibuprofen, ndomethacin, dipyridamole or hydroxychloroquine which interfere with platelet aggregation 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

The safety of Heparin Sodium in 0.9% w/v Sodium Chloride Intravenous Infusion has not been demonstrated in pregnant women.

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 or impairment of fertility.

Animal reproduction studies have not been conducted with heparin sodium. It is not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects: Heparin does not cross the placental barrier.

Heparin is not excreted in human milk.

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
	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 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;	Not known
	Aspartate aminotransferase increased	

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Bleeding is the chief sign of heparin overdosage. Nosebleeds, blood in urine or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Neutralization of heparin effect.

When clinical circumstances (bleeding) require reversal of heparinisation, protamine sulfate (1% solution) by slow infusion will neutralize heparin sodium. **No more than 50 mg** should be administered, **very slowly** in any 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 USP heparin units. The amount of protamine required decreases over time as heparin is metabolized. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about 1/2 hour after intravenous injection. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information the labeling of Protamine Sulfate Injection, USP products should be consulted.

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 inhibiting Factor X and by catalytically accelerating the binding and inactivation of thrombin by antithrombin III.

5.2 Pharmacokinetic properties

Heparin's action commences immediately after administration and lasts up to 6 hours after completion of dose.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened : 15 months

Once removed from the overpouch: Use immediately

Once opened: Use immediately

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

This product is supplied in 500ml plasticised poly (vinyl chloride) (PVC) infusion bags. Each unit is sealed into a high density polyethylene or polypropylene overpouch.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Do not use unless solution is clear and the container is undamaged.
No antimicrobial preservative present. Discard any unused portion.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.,
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IP24 3SE,
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8 MARKETING AUTHORISATION NUMBER

PA 0167/067/001

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10 DATE OF REVISION OF THE TEXT

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