SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Heparin Sodium BP 2000 IU/L in 0.9% w/v Sodium Chloride IV Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin Sodium BP	2000 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

Administration
Administration is by intravenous infusion.
Ensure that the correct formulation is being used, prior to administration of the drug

Dosage
Dosage, rate, and duration of administration are to be individualized and depend upon the indication for use, the patient's age, weight, clinical condition and concomitant treatment, and on the patient's clinical and laboratory response to the treatment. Dosage of heparin should be titrated against patient response.

Heparinisation for dialysis procedures
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.

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 severe thrombocytopenia
- who have had a previous diagnosis of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis (HITT).within the previous 6 months, and while they test positive for HIT antibodies
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- with an uncontrollable active bleeding state such as haemophilia, except when this is due to disseminated intravascular coagulation
- with known hypersensitivity to heparin or porcine derivatives (see section 4.8) or to any ingredient in the formulation

4.4 Special warnings and precautions for use

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

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.

Warnings
Haemorrhage

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, e.g., gastrointestinal bleeding with hematemesis and melena, or haematuria. Fatal haemorrhages have occurred. An unexplained fall in fall in , blood pressure, anaemia and fall in haematocrit, or any other unexplained symptom should lead to serious consideration of haemorrhagic event. (See section 4.8 Adverse Reactions). Haematocrit testing and tests for occult blood in stools should be performed periodically during heparin administration.

Heparin sodium should be used with extreme caution in disease states in which there is increased danger of haemorrhage, including:

- Cardiovascular - subacute bacterial endocarditis. Severe hypertension.

- Surgical - during and immediately following (a) spinal tap or spinal anaesthesia 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. It should be appreciated that gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. (See section 4.8 Adverse Reactions).

- Antithrombin III deficiency may be acquired or inherited. Patients with hereditary antithrombin III deficiency receiving concurrent antithrombin III therapy. (See section 4.5)
- Hepatic: liver disease with impaired haemostasis.
- Thrombocytopenia is commonly seen in patients receiving heparin.Other – menstruation

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

Heparin-induced Thrombocytopenia (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 sources (including heparin flushes) should be discontinued and an alternative anticoagulant used. Future use of heparin, 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, or platelet activation induced by heparin. Platelet counts should be obtained at baseline and periodically during heparin administration. 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 in heparin–naive individuals, and reach a threshold by days 7 to 14. In contrast, “rapid onset” HIT can occur very quickly (within 24 hours following heparin initiation), especially in patients with a recent exposure to heparin (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/mm^3 or if recurrent thrombosis develops, the administration of heparin should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Delayed Onset of Heparin-induced Thrombocytopenia (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 should be evaluated for HIT (with or without thrombosis).

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of up to 30%. It can occur 2 to 20 days (average 5 to 9) following the onset of heparin therapy. Platelet counts should be obtained at baseline and periodically during heparin administration. Mild thrombocytopenia (count greater than 100,000/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/mm^3 or if recurrent thrombosis develops (see Heparin-induced Thrombocytopenia (HIT) With or Without Thrombosis), heparin should be discontinued and, if necessary, an alternative anticoagulant administered.

Heparin Resistance

Increased resistance to heparin is frequently encountered in patients with fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and postsurgical. Monitor coagulation tests closely in such patients. It may be necessary to adjust the dose of heparin based on anti-Factor Xa levels.

Hypersensitivity

Hypersensitivity reactions with chills, fever and urticaria as the most usual manifestations and also asthma, rhinitis, lacrimation, and anaphylactoid reactions have been reported.

Vasospastic Reactions

Vasospastic reactions may develop independent of the origin of heparin, 6 to 10 days after the initiation of the therapy and last for 4 to 6 hours. The affected limb is painful, ischemic and cyanosed. An artery to this limb may have been recently catheterized. After repeat injections, the reaction may gradually increase to include generalized vasospasm, with cyanosis, tachypnoea, feeling of oppression and headache.

Hyperkalaemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients 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 upon discontinuation of heparin.

Plasma potassium should be measured in patients at risk of hyperkalaemia before starting heparin therapy and periodically in all patients treated for more than 7 days.

Fluid balance

The intravenous administration of Heparin sodium in 0.9% Sodium Chloride infusion can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states, or pulmonary oedema.

Solutions containing sodium ions should be used with great care in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there exists oedema with sodium retention.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance and electrolyte concentration and acid base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such an evaluation.

Precautions

Risk of Air Embolism
Do not connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container.
Pressurizing intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.
Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

Solutions Containing Sodium
Solutions containing sodium should be used with caution in patients receiving corticosteroids or corticotrophin.

Monitoring and Laboratory Tests
Periodic platelet counts, haematocrits, coagulation testing and tests for occult blood in stool are recommended during the course of heparin therapy.

Investigations
Elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of 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, elevation of these enzymes in patients receiving heparin should be interpreted with caution.

Use in Paediatric Patients
There have been no studies performed by Baxter Healthcare Corporation in the paediatric population.

Geriatric Use
A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Lower doses of heparin may be indicated in patients over 60 years of age.

Use in Patients with Renal and Hepatic Impairment
Heparin sodium in 0.9% Sodium Chloride infusion should be used with caution in the patients with hepatic or renal disease.

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

4.5 Interaction with other medicinal products and other forms of interaction

Oral Anticoagulants

Heparin may prolong the one-stage prothrombin time. When heparin is given concomitantly with dicumarol or warfarin sodium, wait at least 5 hours after the last intravenous dose before taking a blood sample.

Platelet Inhibitors

Drugs such as NSAIDS (e.g., acetylsalicylic acid, ibuprofen, indomethacin, and celecoxib), epoprostenol, , thienopyridines (e.g. clopidogrel, prasugrel), dipyridamole, hydroxychloroquine, glycoprotein IIb/IIIa antagonists (including abciximab, eptifibatide, and tirofiban), and others that interfere with platelet-aggregation reactions (the main haemostatic defence of heparinized patients), may induce bleeding and should be used with caution in patients receiving heparin.

Other Interactions

Tobacco smoke and nicotine may decrease the anticoagulant effects of heparin. Increased doses of heparin may be required in smokers.

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

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

When administering Heparin sodium in 0.9% Sodium Chloride infusion concomitantly with the drugs listed above monitor coagulation tests frequently and adjust dose as necessary.

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 (≥ 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, Gastrointestinal haemorrhage, Adrenal haemorrhage, Retroperitoneal haemorrhage, Epistaxis, Contusion, Vasospastic reactions (including episodes of painful, ischemic, and cyanosed limbs).	Not known
Blood and lymphatic system disorders	Thrombocytopenia, Heparin-Induced Thrombocytopenia (with or without Thrombosis)	Not known
Renal and urinary disorders	Haematuria	Not known

System Organ Class (SOC)	MedDRA Preferred Term	Frequency
Endocrine disorders	Hypoaldosteronism, Adrenal insufficiency	Not known
Skin and subcutaneous tissue disorders	Skin necrosis, Alopecia	Not known
Musculoskeletal, connective tissue and bone disorders	Osteoporosis	Not known
Immune system disorders	Hypersensitivity, including Anaphylactic shock, Anaphylactoid reaction, Asthma, Chills, Fever, Urticaria, Rhinitis, Lacrimation, Headache, Nausea, Vomiting, Itching, Burning	Not known
Metabolism and nutrition disorders	Rebound Hyperlipidaemia, Hyperkalaemia	Not known
Reproductive system and breast disorders	Priapism,	Not known
General disorders and administration site conditions	Injection site reaction, Local irritation, Erythema, Mild pain, Hematoma or Ulceration	Not known
Investigations	Increased aspartate aminotransferase (SGOT [S-AST]) and alanine aminotransferase (SGPT [S-ALT]). (See section 4.4 *Investigations*)	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 overdosage.

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 Viaflo 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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