# 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 2000 IU/l
Sodium Chloride 9.0 g/l
Disodium Phosphate dodecahydrate 5.8 g/l
Citric Acid Monohydrate 405 mg/l
This provides: 186 mmol/l Sodium, 154 mmol/l Chloride, 16 mmol/l Phosphate and 2 mmol/l Citrate.

Derived from porcine intestinal mucosa, standardized for use as an anticoagulant, in 0.9% Sodium Chloride.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for infusion
Clear, colourless or straw coloured, sterile non-pyrogenic solution for infusion
Heparin sodium in 0.9% Sodium Chloride has an osmolarity of 322 -358 and a pH of ≈7.0

## 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

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

*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 known hypersensitivity to heparin or porcine derivatives (see section 4.8) or to any ingredient in the formulation

- with severe thrombocytopenia
- with an uncontrollable active bleeding state such as haemophilia, except when this is due to disseminated intravascular coagulation
- with history of heparin-induced thrombocytopenia (HIT) (With or Without Thrombosis) while they test positive for HIT antibodies
- 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**

Warnings

*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 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.

Use this product with caution in disease states in which there is increased risk 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.
- Hematologic: 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.
- Patients with hereditary antithrombin III deficiency receiving concurrent antithrombin III therapy. (See section 4.5 Interactions with Other Medicinal Products and Other Forms of Interactions).
- Hepatic: liver disease with impaired haemostasis.
- Other: menstruation, and in patients with indwelling catheters.

*General Warnings*

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-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 for patients with history of HIT (with or without thrombosis), and while they 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 this product 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
Do not use this product as a "catheter lock flush" product; it is not suitable for this use.
*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.

*Hypokalaemia*
Excessive administration of potassium free solutions may result in significant hypokalaemia.

*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 entire course of heparin therapy.

*Investigations*
Significant 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*
This product 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, clopidogrel, thienopyridines, 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. To reduce the risk of bleeding, a reduction in the dose of antiplatelet agent or heparin is recommended.

*Antithrombin III (human)*
The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. To reduce the risk of bleeding, a reduction in the dose of heparin is recommended during treatment with antithrombin III (human).

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

Intravenous nitroglycerin administered to patients receiving heparin may result in a decrease of the partial thromboplastin time with subsequent rebound effect upon discontinuation of nitroglycerin. Careful monitoring of partial thromboplastin time and adjustment of heparin dosage are recommended during coadministration of heparin and intravenous nitroglycerin.

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

When administering this product concomitantly with the drugs listed above monitor coagulation tests frequently and adjust dose as necessary.

**4.6 Fertility, pregnancy and lactation**

There are no adequate data from the use of this product in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each patient before prescribing this product.
Heparin does not cross the placental barrier.
Heparin is not excreted in human milk and can be used during breast-feeding.

**4.7 Effects on ability to drive and use machines**

There is no information on the effects of this product on the ability to operate an automobile or other heavy machinery.

**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 |
| 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 | Hyperlipidaemia, Rebound hyperlipemia, Hyperkalaemia. | Not Known |
| Reproductive System and Breast Disorders | Priapism, Ovarian cyst (corpus luteum haemorrhage) | 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 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**

An overdose requires immediate medical attention and treatment. Bleeding is the primary sign of heparin overdose. Easy bruising, petechial formations, nosebleeds, blood in urine or tarry stools may be the first signs or symptoms of a heparin overdose.
If reversal of heparinization is desired or in the case of overdosage, administer protamine sulfate (1% solution) by slow infusion over a 10 minute period. A maximum of 50 mg should be given in any one dose. 1mg of protamine sulfate neutralizes approximately 100 international units of heparin sodium
Decreasing amounts of protamine are required as time from the last heparin injection increases. Ideally, the dose required to neutralise the action of heparin should be guided by blood coagulation tests or calculated from a protamine neutralisation test.

Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. For additional information the labelling of protamine sulfate products should be consulted. 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.

Blood or plasma transfusions may be necessary; these dilute but do not neutralize 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 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**

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.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Water for injections.

**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**

Because dosages of this drug are titrated to response, no additives should be made to this product.

This product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer unless the solution is clear and colourless, and the seal is intact.

For single use only.
Discard any unused portion.
Do not reconnect partially used bags.
No antimicrobial preservative present.

**7 MARKETING AUTHORISATION HOLDER**

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

**8 MARKETING AUTHORISATION NUMBER**

PA2299/014/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 06 June 1984

Date of last renewal: 06 June 2009

**10 DATE OF REVISION OF THE TEXT**

June 2023