SUMMARY OF PRODUCT CHARACTERISTICS
HEPARIN INJECTION BP

1. Name of the Medicinal Product

1.1 Product Name: Heparin Injection BP

1.2 Strength: 5000 IU/mL

1.3 Pharmaceutical Dosage Form: Sterile Solution for Injection

2. Qualitative and quantitative composition

2.1 Qualitative Declaration

In terms of the active substance(s)

Sterile Solution for Injection - 5 mL Vial

Each Vial contains 25000 IU of Heparin Sodium BP

INN : Heparin Sodium

ATC code : BO1AB01

Heparin sodium is a preparation containing the sodium salt of a sulphated glucosaminoglycan present in mammalian tissues. On complete hydrolysis, it liberates D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulphuric acid. It has the characteristic property of delaying the clotting of freshly shed blood. The potency of heparin sodium intended for parenteral administration is not less than 150 IU/mg, calculated with reference to the dried substance. The potency of heparin sodium not intended for parenteral administration is not less than 110 IU/mg, calculated with reference to the dried substance.

Quantitative Declaration (Qualitative and Quantitative formula per unit)

Component	Reference to Quality Standard	Function	Theoretical Amount Per Unit
Heparin Sodium	BP	Active Ingredient	25000 IU
Benzyl Alcohol	BP	Preservative	0.95% w/v
Hydrochloric Acid	BP	Acidifying Agent	q.s.
Sodium Hydroxide	BP	Alkalizing Agent	q.s.
Water for Injections	BP	Solvent	q.s. to 5 mL

3. Pharmaceutical Form

Sterile Solution for Injection

4. Clinical Particulars

4.1 Therapeutic indications

- For anticoagulant therapy in Prophylaxis & Treatment in Venous Thrombosis & its extension.
- For prophylaxis and treatment of pulmonary embolism;
- In Atrial fibrillation with Embolization;
- For Diagnosis and treatment of Chronic consumptive coagulopathies;
- For prevention of clotting in arterial and heart surgery;
- For prevention of cerebral thrombosis in evolving stroke;
- As an adjunct in treatment of coronary occlusion with acute myocardial infarction;
- As an adjunct in prophylaxis and treatment of peripheral arterial embolism;
- As a general anticoagulant in
  - Blood transfusions
  - Extra corporeal circulation
  - Dialysis procedures and
  - Blood samples for Laboratory purposes.

4.2 Posology and method of administration

Heparin is not effective by oral administration and should be given by deep subcutaneous (intrafat, i.e., above iliac crest or abdominal fat layer) injection; by intermittent IV injection; or intravenous infusion. Intramuscular injection is not usually used. The dosage of Heparin should be adjusted according to the patients coagulation test, which, during the first day of treatment should be determined just prior to each injection. Dosage is considered adequate when the clotting time is elevated approximately 2 .5 to 3 times the control value.

When Heparin Sodium is given by continuous intravenous infusion, the coagulation test should be determined approximately every four hours in the early stages of treatment. When administered intermittently by intravenous, intramuscular, or deep subcutaneous (intrafat) injection, it is desirable to determine the coagulation test before each injection. When a prothrombin depressant is administered with Heparin Sodium coagulation tests and prothrombin activity should be determined at the start of therapy. For immediate anti-coagulant effect, administer Heparin Sodium in the usual therapeutic dosage.

When the results of the initial prothrombin determination are known, administer the first dose of prothrombin depressant in the usual initial amount. Thereafter, perform a coagulation test and the prothrombin activity at appropriate intervals. A period of from four to five hours after the last intravenous dose and 12 to 24 hours after the last subcutaneous (intrafat) dose of Heparin Sodium should elapse before blood is drawn, if a valid prothrombin time is to be obtained. When the prothrombin depressant shows full effect and prothrombin activity is in the desired therapeutic range Heparin Sodium may be discontinued and therapy continued with the prothrombin depressant.

Method of administration	Frequency	Recommended dose
Deep, Subcutaneous (intrafat) Injection	Initial dose	5,000 units by IV injection followed by 10,000 – 20,000 units of a concentrated solution, subcutaneously
A Different site should be used for each injection to prevent the development of massive hematoma.	Every 8 hours (or) Every 12 hours	8,000 – 10,000 units of a concentrated solution 15,000 – 20,000 units of a concentrated solution
Intermittent, Intravenous injection	Initial dose Every 4 to 6 hours	10,000 units, either undiluted or in 50 – 100 mL isotonic sodium chloride injection 5,000 - 10,000 units, either undiluted or in 50 – 100 mL isotonic sodium chloride injection
Intravenous infusion	Initial dose Continuous	5,000 units by IV injection 20,000 – 40,000 units in 1,000 mL of isotonic sodium chloride solution for infusion/day

Although dosage must be adjusted for the individual patient based upon suitable laboratory tests, the following may be used as guidelines for achieving therapeutic anticoagulant effect with Heparin:

a) By deep subcutaneous (intrafat) or, if necessary, intramuscular injection: After an initial I.V. injection, inject 10,000 to 20,000 units of a concentrated Heparin Sodium solution subcutaneously followed by 8,000 to 10,000 units subcutaneously every 8 hours or 15,000 to 20,000 units every 12 hours.
b) By intermittent intravenous infusion: 10,000units initially, then 5,000 to 10,000 units every four to six hours. These amounts may be given either undiluted or diluted with 50 to 100 mL of isotonic sodium chloride injection.
c) By continuous intravenous infusion: Add 20,000 to 40,000 units of Heparin Sodium to 1,000 mL of the solution for infusion. For most patients, the rate of flow should be adjusted to deliver approximately 20,000 to 40, 000 units in 24 hours.

Pediatric Use:
Follow recommendations of appropriate pediatric reference texts. In general, the following dosage schedule may be used as a guideline.
Initial Dose: 50 units/kg (I.V., drip).
Maintenance Dose: 100 units/kg (I.V., drip) every four hours or 20,000 units/M^2/24 hours continuously.

Surgery of the Heart and Blood Vessels:
Patients undergoing total body perfusion for open-heart surgery should receive an initial dose of not less than 150 units of Heparin Sodium per kilogram of body weight. Frequently, a dose of 300 units of Heparin Sodium per kilogram of body weight is used

for procedures estimated to last less than 60 minutes; or 400 units/kilogram for those estimated to last longer than 60 minutes.

Low-Dose Prophylaxis of Postoperative Thromboembolism:
A number of well-controlled clinical trials have demonstrated that low-dose Heparin prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep-vein thrombosis in the legs, as measured by the 1-125 fibrinogen technique and venography, and of clinical pulmonary embolism. The most widely used dosage has been 5,000 units 2 hours before surgery and 5,000 units every 8 to 12 hours thereafter for 7 days or until the patient is fully ambulatory, whichever is longer. The Heparin is given by deep, subcutaneous injection in the arm or abdomen with a fine needle (25 to 26 gauges) to minimize tissue trauma. A concentrated solution of Heparin sodium is recommended.

Such prophylaxis should be reserved for patients over 40 undergoing major surgery. Patients with bleeding disorders, those having neurosurgery, spinal anesthesia, eye surgery, or potentially sanguineous operations should be excluded, as well as patients receiving oral anticoagulants or platelet active drugs. The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or postoperatively should be borne in mind. If such bleeding occurs, discontinuance of Heparin and neutralization with Protamine Sulfate is advisable. If clinical evidence of thromboembolism develops despite low-dose prophylaxis, full therapeutic doses of anticoagulants should be given unless contraindicated. All patients should be screened prior to heparinization to rule out bleeding disorders, and monitoring should be performed with appropriate coagulation tests just prior to surgery. Coagulation-test values should be normal or only slightly elevated. There is usually no need for daily monitoring of the effect of low-dose Heparin in patients with normal coagulation parameters.

Extracorporeal Dialysis Use:
Follow equipment manufacturer's operating directions carefully.

Blood Transfusion:
Additional of 400 to 600 USP units per 100 mL of whole blood. Usually, 7,500 USP units of Heparin Sodium are added to 100 mL of Sterile Sodium Chloride Injection (or 75,000 USP units per 1,000 mL of Sterile Sodium Chloride Injection) and mixed, and from this sterile solution, 6 to 8 mL is added per 100 mL of whole blood.
Laboratory Samples:
Addition of 70 to 150 units of Heparin Sodium per 10 to 20 mL sample of whole blood is usually employed to prevent coagulation of the sample. Leukocyte counts should be performed on heparinized blood within two hours after addition of the Heparin. Heparinized blood should not be used for isoagglutinin, complement, erythrocyte fragility tests, or platelet counts.

4.3 Contra-indications

Heparin Sodium should not be used in patients:
With severe thrombocytopenia; in whom suitable blood - coagulation tests - e.g., the whole blood clotting time, partial thromboplastin time, etc – cannot be performed at appropriate intervals (this contraindication refers to full-dose Heparin; there is usually no need to monitor coagulation parameters in patients receiving low - dose Heparin); with an

uncontrollable active bleeding state, except when this is due to disseminated intravascular coagulation.

4.4 Special warnings and precautions for use

Heparin is not intended for intramuscular use.

Heparin Resistance:

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

Increased Risk in Older Women:
A higher incidence of bleeding has been reported in women over 60 years of age.

White-clot Syndrome:
It has been reported that patients on Heparin may develop new thrombus formation in association with thrombocytopenia, resulting from irreversible aggregation of platelets induced by Heparin, the so-called "white-clot syndrome." The process may lead to severe thromboembolic complications like skin necrosis gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. Therefore, Heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

4.5 Interaction with other medicaments and other forms of interaction

Drugs Affecting Platelet Function:
Drugs that effect platelet function (e.g., Aspirin and other Nonsteroidal anti – inflammatory agents, Dextran, Dipyridamole, GP IIb/IIIa – receptor inhibitor such as Abciximab, Eptifibatide, and Tirofiban) may increase the risk of hemorrhage and should be used with caution in patients receiving Heparin.

Thrombolytic Agents:
Concomitant therapy with Heparin and/or platelet- aggregation inhibitors has been used with thrombolytic agents to prevent reocclusion following lysis of coronary artery thrombi. However, since such therapy has not been shown to be of unequivocal benefit and may increase the risk of bleeding complications, use of anticoagulants concomitantly with thrombolytic therapy should be individualized and careful monitoring is advised. Some evidence suggests a narrow margin of safety for upward adjustment of Heparin dosage, and the need for serial monitoring of Activated Partial Thromboplastin Time (APTT), in patients receiving Heparin concurrently with thrombolytic therapy for acute myocardial infarction.

Dihydroergotamine Mesylate:
When used in combination with Heparin, Dihydroergotamine appears to potentiate the antithrombogenic effects of Heparin by helping to reduce factors that contribute to venous thrombus formation. As a result of its vasoconstrictor effect, Dihydroergotamine accelerates venous return, reduce venous stasis and pooling, and may also indirectly help to prevent damage to venous endothelium caused by excessive dilation, Therefore concomitant use of Dihydroergotamine and Heparin may help to prevent deep – vein thrombosis.

Concomitant subcutaneous administration of Dihydroergotamine Mesylate with Heparin sodium does not appear to affect the pharmacokinetics of Heparin. Concomitant subcutaneous administration of the drugs reportedly decreases peak plasma concentrations of Dihydroergotamine and decreases the rate of absorption of Dihydroergotamine compared with administration of Dihydroergotamine alone; however, the area under the concentration – time curve of Dihydroergotamine is generally unaffected.

4.6 Pregnancy and lactation

Heparin injection should be used with caution during pregnancy, especially during the last trimester (even though heparin does not cross the placenta barrier) and in the immediate post pattern period. It should also be used with caution in the presence of mild hepatic or renal disease, hypertension, during menstruation, or in patients with in – dwelling catheters. A higher incidence of bleeding may be seen in women over 60 years of age.

4.7 Effects on ability to drive and use machines

Heparin has no or negligible influence on the ability to drive or use machines

4.8 Undesirable effects

Hemorrhage:
Hemorrhage 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 with drawing 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 hemorrhagic complications may be difficult to detect. Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patient who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory conformation of the diagnosis, since any delay in an acute situation may result in the patient's death.

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

Local Irritation:
Local irritation, erythema, mild pain, hematoma, or ulceration may follow deep, subcutaneous (intrafat) injection of Heparin Sodium. These complications are much more common after intramuscular use, and such use is not recommended

Hypersensitivity:
Generalized hypersensitivity reactions have been reported, with chills, fever and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and

vomiting and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar side of the feet, may occur.

Thrombocytopenia has been reported to occur in patients receiving Heparin with a reported incidence of 0 to 30%. While often mild and no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications, such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possibly death.

Certain episodes of painful, ischemic and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are, in fact, identical to the thrombocytopenia associated complications remains be determined.

Allergic Conditions:
Because Heparin Sodium injection is derived from animal tissue, it should be used with caution in patients with a history of allergy. Before a therapeutic dose is given to such a patient a trial dose of 1000 units may be advisable.

Miscellaneous:
Osteoporosis following long-term administration of high doses of Heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia priapism, and rebound hyperlipemia on discontinuation of Heparin sodium have also been reported. 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.

4.9 Overdose

Protamine Sulphate (1% solution) by slow infusion will neutralize Heparin. Not more than 50 mg should be given in any 10 minute period.
Each mg of Protamine Sulphate neutralize approximately 100 units of Heparin.
Decreasing amounts of Protamine Sulphate is required as the time for the last Heparin injection increases. Thirty minutes after dose of Heparin approximately 0.5 mg. of Protamine is sufficient to neutralize each 120 units of administered Heparin. Blood or plasma transfusions may be necessary; these dilute but do not neutralize Heparin.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Anti Coagulant Agent

Mechanism of action and Pharmacodynamic effects:
Pharmacodynamic Effects:
Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both in vitro and in vivo. Heparin acts at multiple sites in the normal coagulation system. Small amounts of Heparin in combination with anti thrombin III (Heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of Heparin can inhibit further coagulation by inactivating thrombin and

preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by Heparin. Clotting time is prolonged by full therapeutic doses of Heparin; in most cases it is not measurably affected by low doses of Heparin.

5.2 Pharmacokinetic properties

General characteristics of the active substance

Drug Absorption, Distribution, Biotransformation and Excretion:

Absorption

Heparin is not absorbed from the GI tract and must be administrated parenterally. The onset of anticoagulant activity is immediate following direct I.V. injection or the start of continuous I.V. infusion of full doses of Heparin. There may be considerable inter-patient variation in the extent of absorption following deep subcutaneous injection of Heparin; however, onset of activity usually occur with in 20 – 60 minutes. Results of preliminary studies indicate that the rate and extent of absorption are lower following deep subcutaneous injection of heparin calcium than following deep subcutaneous injection of equal doses of Heparin Sodium.

Distribution

Heparin appears to be extensively bound to low–density lipoprotein, globulins, and fibrinogen. The drug does not cross the placenta and is not distributed into milk.

Elimination

The plasma half-life of Heparin averages 1–2 hours in healthy adults. However, the half life of drug increases with increasing doses. Following I.V. administration of Heparin sodium 100, 200, or 400 units/kg, the plasma half–life of the drug averages, 56, 96, and 152 minutes, respectively. Several studies using Heparin Sodium have shown that the drug has a shorter plasma half life in patients with pulmonary embolism than in healthy individuals or patients with other thrombotic disorders. The plasma half-life of the drug is also decreased in patients with liver impairment but may be prolonged in cirrhotic patients. In anephric patient or patients with severe renal impairment, the half-life of Heparin may be slightly prolonged.

The metabolic fate of Heparin has not been fully elucidated, but the drug appears to be removed from the circulation mainly by the reticuloendothelial system and may localize on arterial and venous endothelium. Although there is no reproducible evidence, it has been suggested that Heparin may be partially metabolized in the liver to uroheparin, which is partially desulphated Heparin. A small fraction of each dose of Heparin appears to be excreted in urine as unchanged drug. Heparin is not removed by hemodialysis.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber.

6 Pharmaceutical particulars

6.1 List of excipients

Benzyl Alcohol BP
Hydrochloric Acid BP
Sodium Hydroxide BP
Water for Injections BP

6.2 Incompatibilities

Heparin has been reported to be incompatible in aqueous solution with certain substances, e.g. some antibiotics, Hydrocortisone, Phenothiazines, Narcotic analgesics and some Antihistamines.

6.3 Shelf-life

- Shelf life in the medicinal product as packaged for sale: 36 months
- Shelf life after dilution or reconstitution according to directions: 24 hours at 30°C with the evaluated diluent 0.9% Sodium Chloride Injection.
- Shelf life after first opening the container: Not applicable.

6.4 Special precautions for storage

Store below 30 ºC.

6.5 Nature and contents of the container

Each 5 mL USP type I clear glass Vial contains 25000 IU of Heparin Sodium BP.

6.6 Instructions for use/handling

For parenteral administration. The solution should be withdrawn using aseptical techniques using a sterile needle and syringe. The solution should be used immediately after opening of the Vial. Any remaining solution should be discarded.