For the use of Registered Medical Practitioner, Hospital or a Laboratory Only.

HEPARIN SODIUM INJECTION IP

HEPANIR™* 1000 IU/mL

HEPANIR™* 5000 IU/mL

For IV,IM or SC Use

COMPOSITION:

	HEPANIR ™* 1000 IU/mL	**HEPANIR ™* 5000 IU/mL**
Each mL contains:		
Heparin Sodium IP (Derived from mucosa)	1000 IU	5000 IU
Preservative: Benzyl Alcohol IP	0.95 % w/v	0.95 % w/v

DESCRIPTION:

HEPANIR™* is a heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, having anticoagulant properties. Heparin Sodium Injection IP, is a sterile solution of Heparin Sodium derived from Bovine/Porcine intestinal mucosa, standardized for anticoagulant activity. It is to be administered by intravenous or deep subcutaneous routes. The potency is determined by a biological assay using a reference standard based on units of Heparin activity per milligram.

ACTION AND CLINICAL PHARMACOLOGY:

Pharmacokinetics:

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

Pharmacokinetics:

Pharmacodynamics:

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.

Patients over 60 years of age, following similar doses of heparin, may have higher plasma levels of heparin and longer activated partial thromboplastin times (APTTs) compared with patients under 60 years of age.

Peak plasma levels of Heparin are achieved 2 to 4 hours following subcutaneous administration, although there are considerable individual variations. Log linear plots of heparin plasma concentrations

with time, for a wide range of dose levels, are linear, which suggests the absence of zero order processes. Liver and the reticuloendothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase (t1/2 = 10 min.) and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.
Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

INDICATIONS AND CLINICAL USES:
Heparin Sodium injection is indicated for:
Anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension; low- dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominothoracic surgery or who, for other reasons, are at risk of developing thromboembolic disease. Prophylaxis and treatment of pulmonary embolism; atrial fibrillation with embolization; diagnosis and treatment of acute and chronic
consumptive coagulopathies (disseminated intravascular coagulation); prevention of clotting in arterial and cardiac surgery; prophylaxis and treatment of peripheral arterialembolism. Heparin may also be employed as an anticoagulant in blood transfusions,extracorporeal circulation, and dialysis procedures and in blood samples for laboratory purposes.

DOSAGE AND ADMINISTRATION:
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency.
Confirm the choice of the correct heparin sodium injection vial prior to administration of the drug to a patient. The 1 ml vial must not be confused with a “catheter lock flush” vial or other 1 ml vial of inappropriate strength. When Heparin is added to an infusion solution for continuous intravenous administration, the container should be inverted at least six times to ensure adequate mixing and prevent pooling of the heparin in the solution.
Heparin Sodium is not effective by oral administration and should be given by intermittent intravenous injection, intravenous infusion, or deep subcutaneous (intrafat, i.e., above the iliac crest or abdominal fat layer) injection. The intramuscular route of administration should be avoided because of the frequent occurrence of hematoma at the injection site.
The dosage of heparin sodium should be adjusted according to the patient’s coagulation test results. When heparin is given by continuous intravenous infusion, the coagulation time should be determined approximately every 4 hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each injection during the early stages of treatment and at appropriate intervals thereafter. Dosage is considered adequate when the activated partial thromboplastin time (APTT) is 1.5 to 2 times normal or when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value. After deep subcutaneous (intrafat) injections, tests for adequacy of dosage are best performed on samples drawn 4 to 6 hours after the injection.
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.

Converting to oral anticoagulant:

When an oral anticoagulant of the coumarin or similar type is to begun in patients already receiving heparin sodium, baseline and subsequent tests of prothrombin activity must be determined at a time when heparin activity is too low to affect the prothrombin time. This is about 5 hours after the last intravenous bolus and 24 hours after the last subcutaneous dose.If continuous IV heparin infusion is used, prothrombin time can usually be measured at any time. In converting from Heparin to an oral anticoagulant, the dose of the oral anticoagulant should be the usual initial amount and thereafter prothrombin time should be determined at the usual intervals. To ensure continuous anticoagulation, it is advisable to continue full heparin therapy for several days after the prothrombin time has reached the therapeutic range. Heparin therapy may then be discontinued without tapering.

Therapeutic anticoagulant effect with full-dose Heparin:

Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage schedules may be used as guidelines. For initial deepsubcutaneous (Intrafat) injection the recommended dose (based on 150 lb [68 kg patient]) is 5000 units by IV Injection, followed by 10,000 to 20,000 units of a concentrated solution, subcutaneously after every 8 hours or every 12 hours. A different site should be used for each injection to prevent the development of massive hematoma and the recommended doseis 8000 to 10,000 units of a concentrated solution or 15,000 to 20,000 initial dose units of a concentrated solution. For intermittent intravenous injection the initial dose is10,000 units, either undiluted or in 50 to 100 ml of 0.9 % Sodium Chloride Injection IP and after every 4 to 6 hours the recommended dose is 5000 to 10,000 units, either undiluted or in 50 to 100ml of 0.9 % Sodium Chloride Injection IP. For initial intravenous infusion 5000 units by IV injection and then on continuous 20,000 to 40,000 units/24 hours in 1000 ml of 0.9 % Sodium Chloride Injection IP (or any compatible solution) for infusion.

Pediatric Use

Use preservative-free Heparin Sodium Injection, USP in neonates and infants.

There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience. In general, the following dosage schedule may be used as a guideline in pediatric patients:

Initial Dose 75 to 100 units/kg (IV bolus over 10 minutes)

Maintenance Dose:

Infants: 25 to 30 units/ kg/ hour;

Infants <2 months have the highest requirements (average 28 units/kg/hour)

Children >1 year of age: 18 to 20 units/ kg/ hour;

Older children may require less heparin, similar to weight-adjusted adult dosage

Monitoring:

Adjust heparin to maintain a PTT of 60 to 85 seconds, assuming this reflects an anti-Factor Xa level of 0.35 to 0.70

Geriatric Use: Patients over 60 years of age may require lower doses of heparin.

Surgery of the heart and blood vessels: Patients are 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 per kilogram is used for procedures estimated to last less than 60 minutes, or 400 units per kilogram for those estimated to last longer than 60 minutes.

Low-dose prophylaxis of postoperative thromboembolism:
The most widely used dosage has been 5000 units 2 hours before surgery and 5000 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-gauge) to minimize tissue trauma.
A concentrated solution of Heparin Sodium is recommended. Such prophylaxis should be reserved for patients over the age of 40 who are undergoing major surgery. Patients with bleeding disorders and those having neurosurgery, spinal anesthesia, eye surgery or potentially sanguineous operations should be excluded, as should 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 sulphate are 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 giving heparin 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: Follow equipment manufacturers operating directions carefully.

Blood Transfusion: Addition of 400 to 600 USP units per 100 ml of whole blood is usually employed to prevent coagulation.Usually, 7500 USP units of Heparin Sodium are added to 100 ml of 0.9 % Sodium Chloride Injection, (or 75,000 USP units per 1000 ml of 0.9 % Sodium Chloride Injection IP) and mixed; from this sterile solution, 6 to 8 ml are 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 2 hours after addition of the heparin. Heparinized blood should not be used for isoagglutinin, complement, or erythrocyte fragilitytests or platelet counts.

CONTRA-INDICATIONS:
Heparin Sodium should not be used in patients with the following conditions:
- Severe thrombocytopenia.
- When 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);

- An uncontrolled active bleeding state, except when this is due to disseminated intravascular coagulation.

WARNING IN CLINICAL STATES :

Fatal medication errors:

Do not use Heparin Sodium Injection as a "catheter lock flush" product. Heparin Sodium Injection is supplied in vials containing various strengths of heparin, including vials that contain a highly concentrated solution of 10,000 units in 1 ml. Fatal hemorrhages have occurred in pediatric patients due to medication errors in which 1 ml Heparin Sodium Injection vials were confused with 1 ml "catheter lock flush" vials. Carefully examine all Heparin Sodium Injection vials to confirm the correct vial choice prior to administration of the drug.

Hypersensitivity: Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations.

Hemorrhage: 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 a 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.

Coagulation Testing: When Heparin Sodium is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if hemorrhage occurs, heparin sodium should be promptly discontinued

Thrombocytopenia: Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. Platelet counts should be obtained at baseline and periodically during heparin administration. 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 (see heparin- induced thrombocytopenia and thrombosis), the heparin product should be discontinued, and, if necessary, an alternative anticoagulant administered.

Heparin - Induced Thrombocytopenia (HIT) And Heparin - Induced Thrombocytopenia Thrombosis (HITT): Heparin –induced Thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as Heparin-Induced Thrombocytopenia and Thrombosis (HITT). Thrombotic events may also be the initial presentation for HITT. 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 possibly death. 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 promptly discontinued and, alternative anticoagulants considered, if patients require continued anticoagulation.

Delayed onset of HIT and HITT: Heparin –induced Thrombocytopenia and Heparin –induced Thrombocytopenia and 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 and HITT.

Benzyl Alcohol Toxicity

Use preservative-free Heparin Sodium Injection in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death in pediatric patients. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants may be more likely to develop toxicity

Use In Neonates: This product contains the preservative benzyl alcohol and is not recommended for use in neonates. There have been reports of fatal 'gasping syndrome' in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Carefully examine all Heparin Sodium Injection vials to confirm choice of the correct strength prior to administration of the drug. Paediatric patients, including neonates, have died as a result of medication errors in which Heparin Sodium Injection vials have been confused with "catheter lock flush" vials. (See warnings, Fatal Medication Errors).

PRECAUTIONS:

General: In Thrombocytopenia, heparin-induced Thrombocytopenia (HIT) and Heparin – induced Thrombocytopenia and Thrombosis (HITT)

Heparin Resistance:

Increased resistance to Heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections having thrombosis tendencies, myocardial infarction, cancer and in post-surgical patients.

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

Laboratory Tests: 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.

Carcinogenesis, mutagenesis, impairment of fertility: No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin. Also, no reproduction studies in animal have been performed concerning mutagenesis or impairment of fertility.

Pregnancy: Teratogenic effects-Pregnancy category C. Animal reproduction studies have not been conducted with Heparin Sodium. It is also 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.

Non teratogenic effects: Heparin does not cross the placental barrier.

Nursing mothers: Heparin is not excreted in human milk.

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

DRUG INTERACTIONS:

Oral Anticoagulants: Heparin Sodium may prolong the one-stage prothrombin time. Therefore, when Heparin Sodium is given with Dicumarol or Warfarin sodium, a period of at least 5 hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood is drawn, if a valid prothrombin time is to be obtained.

Platelet Inhibitors: Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet – aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other Interaction: Digitalis, tetracyclines, nicotine or antihistamines may partially counteract the anticoagulant action of Heparin Sodium. Intravenous nitroglycerin administered to heparinized patients 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 co-administration of heparin and intravenous nitroglycerin.

Drug/laboratory Tests Interactions:

Hyperaminotransferasemia: 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, increases that might be caused by drugs (like heparin) should be interpreted with caution.

ADVERSE REACTIONS:

Hemorrhage: Hemorrhage is the main 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 hemorrhagic complications may be difficult to detect:

a. Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant the Therefore, such treatment should be discontinued in patients who develop signs and Symptoms of acute adrenal hemorrhage 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.

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

c. Retroperitoneal hemorrhage.

Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) and Heparin –induced Thrombocytopenia and Thrombosis (HITT) and delayed Onset of HIT and HITT.

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, ocurring 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 of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complication 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 to be determined.

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 hyperlipidemia 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.

SYMPTOMS AND TREATMENT OF OVERDOSE:

Symptoms: 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.

Treatment: When clinical circumstances (bleeding) require reversal of Heparinization, 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 ½ hour after intravenous injection.
Administration of protamine sulfate can cause severe hypotensive and anaphylactic reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available.
For additional information consult the labeling of Protamine Sulfate Injection, USP products.

PRESENTATION:
HEPANIR™* is available as HEPANIR™* - 5000 IU/5mL
HEPANIR™* - 25000 IU/5mL in 5mL glass vial with flip of seal.

STORAGE:
Store at a temperature not exceeding 30° C.

ACULIFE®
Manufactured in India by:
Aculife Healthcare Pvt. Ltd.
Sachana, Gujarat 382150, India.

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