Size : L- 120 x H-170mm Front

Size : L- 120 x H-170mm Back

Summary of Product Characteristics

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Heparin Sodium Injection IP 5,000 IU/5ml

Hepathin Injection **5000**

Composition :
Each ml contains :
Heparin Sodium IP 1,000 IU
Water for Injections IP q.s.

1. Name of medicinal product Active ingredient: Heparin Sodium

Heparin Sodium

2. Prescription status
Prescription only medicine

3. Qualitative and quantitative composition

3.1 Pharmacotherapeutic group
Anticoagulant

3.2. Active ingredients by class and quantity

3.2.1 Medically active ingredients:
1 ml solution for injection contains 5,000 (I.U.) Heparin Sodium (from porcine intestinal mucosa)
Activity: min 150 I.U./ mg, max. 200 I.U./ mg ≙ 25.0 - 33.3 mg

3.2.2 Other active ingredients:
1 ml solution for injection contains 10 mg benzyl alcohol

3.3 Other ingredients:
Sodium Chloride, Water for Injections

4. Indications
Treatment of thrombo-embolic disorders as deep vein thrombosis, acute arterial embolism or thrombosis, thrombophlebitis, pulmonary embolism, fat embolism.
Prophylaxis of deep vein thrombosis and thromboembolic events.

5. Contraindications

Absolute contraindications
Heparin allergy or hypersensitivity to other components of the preparation HEPARIN INJECTION IP 5,000 UNITS/ML
Patients with present or previous thrombocytopenia (type II) caused by heparin
Diseases accompanied by increased bleeding tendency e.g. hemorrhagic diathesis, clotting factor deficiencies (except disseminated intravascular coagulation during the phase of hypercoagulation) severe hepatic, renal or pancreatic diseases, severe thrombocytopenia
Diseases with a suspicion of damage to the vascular system, such as: gastric ulcers and/or intestinal ulcers, hypertension (above 105 mmHg diastolic), intra-cerebral hemorrhage, injury or surgery of the central nervous system, eye surgeries, retinopathy (severe retina problems), intravitreal hemorrhage, aneurysm of cerebral arteries, sub-acute bacterial endocarditis (inflammation of the endocardium)
Risk of miscarriage (Abortus immensis)
Spinal anaesthesia, epidural anaesthesia, lumbar puncture

Relative contraindications
Suspicion of a malignant disease with tendency to hemorrhages
Renal and urethral calculi
Chronic alcoholism

An especially meticulous medical monitoring is required:
During pregnancy, especially in case of long term use
In elderly patients, especially women
When concomitantly treated with fibrinolytics or oral anticoagulants, with platelet aggregation inhibitors (for example Acetyl Salicylic Acid, Ticlopidin, Clopidrogrel) and/or Glycoprotein IIb/IIIa receptor antagonists.
When concomitantly treated with drugs that increase serum potassium level. The serum potassium level should be monitored in high-risk patients (patients with increased risk of hyperkalemia such as diabetes mellitus, impaired renal function or treatment with serum-potassium level raising medication).

Warnings:
Because of its benzyl alcohol content HEPARIN INJECTION IP 5,000 UNITS/ML must not be used in neonates, especially not in those showing signs of immaturity.

Use in pregnancy and lactation
Heparin does not cross the placenta and does not appear in breast milk. Up to date, no incidence of fetal malformations caused by heparin use in pregnancy has been reported. Increased risk of abortions and stillbirth has been reported. Complications in pregnant women caused by treatment or by the disease itself cannot be excluded.

The use of epidural anaesthesia during labour, for women being medically treated for anticoagulation, is absolutely contraindicated.

6. Side effects
Depending on the dosage of HEPARIN INJECTION IP 5,000 UNITS/ ML, increased hemorrhages especially cutaneous hemorrhages, hemorrhage of the mucous membranes, wounds, in the area of the gastrointestinal tract, the urinary tract and the genitourinary tract should be taken into consideration.

Occasionally at the beginning of the treatment, a slight temporary decrease of the thrombocyte count (Thrombocytopenia Type I) with values between 100,000 and 150,000/µl (caused by a temporary activation of the thrombocytes) can be observed. Complications usually do not occur. The treatment can therefore be continued.

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. If the count falls below 100,000/mm³ or if recurrent thrombosis develops (see Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis), the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

The patient must be informed that he must not be treated with drugs containing heparin in the future. Guidelines for use of platelet values: see section 14.

Type II Heparin-induced Thrombocytopenia (HIT) and Type II HIT 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 Type II HIT and Type II HIT and thrombosis.

Often an increase of the serum transaminases (GOT, GPT), the Gamma-GT (gamma glutamyl transpeptidase) as well as LDH (lactic dehydrogenase) and lipase are observed, which in most cases after termination of the treatment with heparin is reversible and clinically insignificant.

Hypersensitivity against heparin and anaphylactic reactions are rare. Single cases of anaphylactic shock have been reported.
This must be taken into account, in particular in patients who have already received heparin in the past.

Allergic reactions include symptoms such as nausea, headaches, fever, articular pains, urticaria, vomiting, pruritus, dyspnea, bronchospasm and decrease of blood pressure.

After the use over a long period of time (months) an increase of osteoporosis could be developed, especially when higher dosages are administered and particularly with patients, who have a tendency thereto.

In rare cases temporary hair loss (alopecia) could occur. After termination of the treatment the hair growth occurs again within reasonable time.

In very rare cases, heparin can induce hypoaldosteronism associated with hyperkalemia and metabolic acidosis, especially in patients with impaired renal function and diabetes mellitus.

In individual cases priapism and vasospasms have been reported.

Local tissue reactions (like for instance stiffness, redness, discoloring and minor hematoma) on the injection site can be observed occasionally.

In rare cases reactions of hypersensitivity due to benzyl alcohol can occur.

7. Interaction with other medicinal products
Substances that can influence plasma blood coagulation or the cells involved in this process may cause a tendency toward increased bleeding. (Such substances are, for example, acetyl salicylic acid, Ticlopidin, Clopidogrel, glycoprotein IIb/IIIa receptor antagonists, coumarine derivatives, fibrinolytics, dipyridamol, dextranes, high dose penicillin therapy). An enhanced heparin effect in concomitant administration of non steroidal anti-inflammatory drugs (such as Phenobutazone, Indomethacin, Sulfinpyrazone) is possible.

When alkaline medications such as tricyclic psychotropics, antihistamines and quinine are concomitantly administered, salt formation with heparin can cause loss of efficacy of both drugs.

An intravenous infusion of nitroglycerine might cause a reduction of the effectiveness of Heparin. A removal of nitroglycerine might cause a rapid increase of aPTT. Close controls of PTT together with a dosage adjustment of Heparin are necessary with the simultaneous infusion of nitroglycerine. An increased effect of other drugs. e.g. Propranolol, can occur through plasma protein binding displacement.

Medication increasing serum potassium levels can only be used under especially close medical monitoring together with HEPARIN INJECTION IP 5,000 UNITS/ML.

In addition, heparin shows numerous interactions with other preparations, whose clinical significance is being evaluated differently.

8. Warnings
With infants, children and patients with kidney and/ or liver insufficiency a meticulous supervision and control of coagulation values is required. The same applies also for thrombo-embolism prophylaxis ("low dose" treatment).

During treatment with HEPARIN INJECTION IP 5,000 UNITS/ML intra-muscular injections are to be avoided due to risk of hematomas.

Patients treated with HEPARIN INJECTION IP 5,000 UNITS/ML (over 22,500 I.U. /day) should avoid all and any risk of being injured.

Heparin induced 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 Heparin-induced Thrombocytopenia and Thrombosis), the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

Type II Heparin-induced Thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. Type II 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 platelet count falls below 100,000/µl or if recurrent thrombosis develops, the heparin product should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Type II Heparin-induced Thrombocytopenia (HIT) and Type II HIT 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 Type II HIT and Type II HIT and thrombosis.

9. Most important incompatibilities
Due to the danger of physical-chemical incompatibilities Heparin may not be administered drawn up with other medication in a hypodermic syringe or an infusion.

10. Single and daily dosage
Heparin must be dosed individually!

The dose depends on the coagulation parameters, nature and course of the disease, the patient's response, side effects, body weight and age. Different heparin sensitivity and the possible development of heparin tolerance during the course of treatment must be taken into account.

1) Thrombo-embolism prophylaxis (low-dose treatment)

For the prophylaxis of thrombo-embolism subcutaneous injection is recommended.

Pre- and postoperative thrombo-embolism prophylaxis:

Preoperative: 5,000 7,500 I.U. subcutaneous approximately 2 hours before the operation.
Postoperative: depending on the risk of thrombosis, usually 5,000 I.U. s.c. every 8 12 hours or 7,500 I.U. every 12 hours until mobilization of patient or until sufficient effect of Vitamin K antagonist. Laboratory diagnostic controls (coagulation times) for the dosage adjustment might be required in individual cases.

PAC3L346-10 / 01.07

Prophylaxis in non-operative medicine:

(For instance in cases of a long time confinement to bed, increased tendency of the patient for thrombosis, diseases with increased risk for thrombosis).

Depending on the risk for thrombosis, usually 5,000 I.U. subcutaneous injection every 8 12 hours or 7,500 I.U. subcutaneous injection every 12 hours.
The dosage must be adjusted to the risk for thrombosis and the activity degree of the coagulation system and may be determined by means of coagulation controls.

2. As part of the treatment of venous and artery thrombo-embolic diseases

In case of continued coagulation within the blood vessels the continuous intravenous administration is recommended.

Dosage in adults: In general beginning with 5,000 I.U. Heparin to be administered as intravenous bolus, followed by a continued infusion with 1,000 I.U. Heparin/ hour by perfusion pump.

Dosage in children: Initially 50 I.U. per kg body weight, followed by 20 I.U. per kg body weight/ hour.

In case a permanent intravenous infusion is not possible, a subcutaneous therapy (divided into 2 3 individual doses) can alternatively be carried out under close therapy control (for instance 10,000 to 12,500 I.U. Heparin every 12 hours)

A close therapy control with the determination of the coagulation parameters is required in any case.

Therapy monitoring and dosage adjustment are being carried out in general with the activated partial thromboplastin time (aPTT), which usually should be increased by 1.5 to 2.5 of the norm. With continuous intravenous administration of Heparin controls are recommended 1 to 2 hours , 6h, 12h and 24h after the beginning of the therapy and with subcutaneous application 6 hours after the administration of the 2nd dose.

Treatment of venous thrombo-embolism

Initially with 5,000 I.U. Heparin to be administered as intravenous bolus, followed by an intravenous infusion with usually 1,000 I.U. Heparin/ hour. The dosage should be adjusted according to the aPTT, whereas a prolongation of the aPTT of 1.5 to 2.5 times of the initial value should be achieved (preferably within the first 24 hours).
The treatment should be done for at least 4 days, or so long as a sufficient oral anti-coagulation has been achieved.

As part of the treatment of unstable angina pectoris or the Non - Q-wave myocardial infarction:

In general 5,000 I.U. Heparin to be administered as intravenous bolus, followed by a continuous infusion with 1,000 I.U. Heparin/ hour. The dosage should be adjusted according to the aPTT, which should be prolonged to 1.5 to 2 times of the normal value.
Heparin should be administered for at least 48 hours.

As accompanying therapy of thrombolysis with fibrin-specific thrombolytic agents (e.g. r-tPA) for the treatment of acute myocardial infarction:

Initially with 5,000 I.U. Heparin to be administered as intravenous bolus, followed by an intravenous infusion of 1,000 I.U. per hour.
The infusion should be adjusted according to the aPTT value to a prolongation of 1.5 to 2.5 times of the initial value. Heparin should be administered for over 48 hours.

In cases of thrombolysis with non-fibrin-specific thrombolytic agents (e.g. streptokinase) it is possible to administer 12,500 I.U. Heparin subcutaneous every 12 hours, starting 4 hours after the thrombolysis.

The exact dosage of the accompanying therapy of Heparin depends on the type of the thrombolytic agents and shall be done in accordance with the specifications for the individual thrombolytic agent. In any case the coagulation status should be monitored closely.

3) Anti coa gulation in a treatment or surgery involving extra-corporeal circulation:

Heart Lung machine: The dosage depends on the type of heart lung machine and the duration of the operation and shall be handled individually.

Hemodialysis: Individual dosage according to the results of the coagulation determinations and the type of machine.

For the determination of the coagulation values the blood must be centrifuged immediately.

11. Posology and route of administration
For the subcutaneous and intravenous injection or diluted for intravenous infusion.

Subcutaneous injection
The insertion should be done with a fine injection needle vertically to the axis of the body into an abdominal skin-fold or into the front side of the thigh; the injection must be strictly subcutaneous. A possible remaining drop on the injection needle must be removed before administrating the injection, as otherwise the insertion of Heparin into the injection canal might cause a superficial hematoma or in rare cases local allergic irritations.

The duration of the application is to be determined by the treating physician. Regular controls of the activated partial thromboplastin time (aPTT) as well as control of the platelet count (see also section 14) are necessary in treatment with heparin.

12. Emergency measures, symptoms and antidotes
Symptoms of an overdose:

In most cases, cutaneous hemorrhage and hemorrhage of the mucous membranes, wounds, the gastro intestinal and genitourinary tract (Epistaxis (nose bleeding) hematuria, melaena, hematomas, petechias). Hypotension, decrease of hematocrits or other symptoms could be signs of an occult hemorrhage.

Therapy measures in cases of overdoses:

In cases of light hemorrhages the Heparin dose can be reduced. In cases of mediocre non - life - threatening hemorrhages the therapy with Heparin should be interrupted. In cases of severe life - threatening hemorrhages, intensive medical measures and the administration of Protamine is required, if other reasons for the hemorrhage (e.g. disseminated intravascular coagulation, lack of factors) can be excluded. Protamine should only be administered in cases of life - threatening hemorrhages, as with complete neutralization of Heparin the risk of a thrombosis exists.
In addition there should be, under intensive medical conditions, a monitoring and possibly correction of the vital parameters, blood transfusions, volume replacement and possibly circulatory therapy with catecholamines.
The antidote Protamine is a protein rich in Arginine, which usually is used as chloride or sulphate. As a rule 1 mg Protamine neutralizes the effect of approximately 100 IU
Heparin. For the therapy the half-life of Heparin and the type of application must be taken into consideration, meaning 90 minutes after an intravenous administration of Heparin only 50% of the calculated amount of Protamine should be administered, 3 hours after the intravenous administration only 25%. In case of over titration Protamine could activate the fibrinolysis and then even cause an intensified readiness for hemorrhages. An intravenous injection of Protamine, administered too fast, could cause hypotension, bradycardia, dyspnea and unpleasant sensations. Protamine is eliminated from the blood faster than Heparin. The effect of the neutralization must be controlled by determining the partial thromboplastine time (PTT) or thrombin time. Heparin cannot be dialized.

13. Pharmacological and toxicological properties, pharmacokinetics and bio-availability data as far as necessary for therapeutic use:

13.1. Pharmacological properties
Heparin is a mucopolysaccharide-polysulphuric acid ester and consists of glucosamine-N-sulphuric acid and sulphuric acid esters of glucuronic acid, which are coupled by glycosidic bonds.
Due to its strong negative charge, heparin forms complexes with certain proteins and their biological characteristics may therefore be altered. This is particularly true for Antithrombin III (AT III), which becomes approximately 700 times more active due to complex binding with heparin.
Activated AT III inhibits serine proteases, a group of substances including the coagulation factors XIIa, XIa, Xa, VIIa and IIa. Factor VIIa is relatively insensitive, IIa (Thrombin) is however extremely sensitive for the effect of the Heparin-AT III-complex. Even small heparin doses accelerate the inactivation of factor IIa (Thrombin) and Xa by AT III. This is the explanation for the prophylactic effect of low-dose heparin in the prevention of thrombo-embolic diseases. The coagulation inhibition depends on the concentrations of AT III and fibrinogen. High heparin doses also inactivate thrombin produced in excess and thus preclude the conversion of fibrinogen to fibrin. Heparin affects platelet functions.

13.2. Toxicological properties
a) Acute toxicity
The toxicity of Heparin is extremely low and depends mainly on its purity grade.
At high concentrations (180,000 I.U./ 100 g) hematomas can be intensified.

b) Chronic / sub-chronic toxicity
Internal bleedings and hematoms were detected in sub-chronic and chronic examinations after intravenous and s.c. applications at different species of animals depending on the dose.

Osteoporotic effects appeared in a 6-months examination on dogs. In animal experiences the wound healing, healing of fractures and re-calcification of bones is delayed by use of Heparin.

c) Mutagenic and tumorigenic potential
No examinations have been performed in respect to the tumorigenic potential. No indices on a mutagenic potential were found in in-vitro and in-vivo examinations on gentoxic effects.
No data are available regarding mutagenicity and cancerogenicity of topically administered Heparin.

d) Reproductive toxicity
Heparin does not cross the placenta. Animal experiences did not show any advice to fetal distress.
No data are available regarding reproductive toxicity of topically administered Heparin

13.3 Pharmacokinetics
Heparin is to be administered subcutaneously or intravenously. Due to its large size of molecules and negative surface charge Heparin is not resorbed by the intestine, an absorption by inhalation is possible. The effect of heparin starts immediately after intravenous application, after subcutaneous application after 20 30 min.. The inter-individual half period varies, the medial half period is specified with 90 120 min. and depends on the dose and hepatic and renal function and the disease pattern. Heparin is bounded extremely to plasma proteins (LDL, globulins (in particular AT III) and fibrinogen), the volume of distribution in adults is specified with approx. 0.07 L/kg. After parenteral administration heparin is eliminated from blood into the reticuloendothalial system by hepatic metabolism (Heparinases) and urinary excretion, predominantly in form of depolymerizied, inactivated heparin. The urinary excretion is effected by glomuleral filtration and by tabular secretion.

14. Further information:
Platelet count controls should be carried out:
Before starting heparin administration
One day after starting heparin administration
Afterwards during first three weeks at regular intervals every three to four days
Furthermore a control of platelet count is recommended at the end of heparin administration.
Heparin may falsify numerous laboratory results, e.g. erythrocyte sedimentation rate, erythrocyte resistance and complement fixation examination.
Heparin may affect the prothrombin time; this must be considered during adjustment to coumarine derivatives. Tests on thyroid function might be falsified during heparin therapy (e.g. false high levels of T3 and T4).

Use in pregnancy

During birth, epidural anaesthesia is absolutely contra-indicated in pregnant women treated with anticoagulants. Coagulation inhibition therapy is contra-indicated in case of increased bleeding tendency (e.g. abortus imminens).
Acute treatment with heparin during pregnancy is controversial for disseminated intravascular coagulation with consumption coagulopathy, e.g. premature abruption of placenta; in this case synthetic antifibrinolytics are currently applied.
Also the usefulness of long-term treatment of pregnant women with heparin to inhibit fibrinogen films for prevention of intra-uterine insufficiency is doubted.
Contraception is to be discussed with all women depending on heparin administration.
Heparin should not be used for a period exceeding three months. During birth the daily dose should not exceed 15,000 I.U.

15. Shelf-life
The shelf-life is 2 years.
This pharmaceutical is not be used after expiry date.

16. Storage :
Store in a cool , dry & dark place.
(Below 30ºC.)

Mfg. Lic. No.: N-MB/16/185

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Mauza Ogli, Sukeli Road, Kala Amb,
Distt. Sirmour-173030 (H.P.)

Marketed by
BIOMAK LABORATORIES PVT.LTD.
(A Division of Urihk Pharmaceutical Pvt. Ltd.)
SCO No.36-37, Sector 17, First Floor
Shopping Complex Huda, Jagadhri
Yamuna Nagar, Haryana, India -135003