EPRIN 1000/5000

EPRIN 1000 (Heparin Injection BP, 1000 IU/ML, 5ML Vial)
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Description
EPRIN 1000 (Heparin Injection BP 1000IU/ML, 5ML Vial) is clear, colorless or faintly straw-colored aqueous solution.
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Pharmacodynamics
Pharmacotherapeutic group: Anti-thrombotic agents, heparin group, ATC code B01A, B01.

Mechanism of action and Pharmacodynamics 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.

Pharmacokinetics
Absorption
Heparin is not absorbed from the GI tract and must be administrated parenterally. The onset of anticoagulant activity is immediate following direct IV injection or the start of continuous IV 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 within 20 – 60 minutes.

Distribution
Heparin is extensively bound to plasma proteins. It does not cross the placenta and is not distributed into milk.

Elimination
The metabolic fate of heparin is not fully understood. No biotransformation in plasma or liver, nor any renal excretory mechanism has been identified as primarily responsible for elimination of the

drug. It has been suggested that transfer and storage in the reticuloendothelial system may play a role, or that heparin may be partially metabolised in the liver. After administration of large doses intravenously, a small fraction of unchanged drug is excreted in the urine.

Indications

Heparin is indicated for prophylaxis and treatment of thrombo-embolic disorder such as thrombophlebitis, pulmonary embolism, myocardial infraction, arterial embolism and other occlusive vascular disease. It is also used to prevent thrombo-embolic complication from cardiac and vascular surgery, dialysis, frostbite and other perfusion procedures. Heparin is also used as anticoagulant in blood transfusions and for laboratory purpose.

Recommended Dose

Express dose in unit only; dose must be individually titrated to desired effect (usually 1.5 -2.5 times control clotting test used).

1. Treatment of venous thrombosis or pulmonary embolus. Duration of therapy is 7-10days, then followed by oral anticoagulation.

i) Continuous IV solution : 50-100 units/kg initially : then 10-15 units/kg/hr (venous thrombosis) or 20 unit/kg/hr (pulmonary embolus)

ii) Intermittent IV: 75-125 units/kg q 4hr.

iii) Subcutaneous: 10,000 – 20,000 units initially (proceeded by a 5000 units IV loading dose), then 8000-10,000 unit q 8hr or 15,000-20,000 units q 12hr.

2. SC for prophylaxis of deep vein thrombosis (low-dose) 5000 units 2hr before surgery, repeated q 8-12hr until patient is ambulatory.
3. IV for heparin lock flush inject sufficient solution (of 10-100 units/ml) into injection hub to fill the entire after each heparin lock use.
4. Haemodialysis: 7500 -12,500 IU is normally required per dialysis.
5. Myocardial infraction: 5,000 IU s.c every 12hours beginning during the 12hours following the first sign of myocardial infraction.

Route of Administration

Subcutaneous or intravenous use. Heparin Injection BP is administered by subcutaneous or intravenous injection or by intravenous infusion after dilution with a suitable vehicle solution.

Contraindications

Heparin Sodium should not be used in patients:
Hypersensitivity to heparin or to any of the excipient of Heparin Injection BP 1000 IU/mL and 5000 IU/mL.

Heparin-induced thrombocytopenia (type II) either known from the patient's history or being suspected on grounds of clinical observations such as occurrence of thrombocytopenia or new arterial and/or venous thromo-embolic complications during therapy.

Disease associated with haemorrhagic diathesis, such as:

- Coagulopathies
- Thrombocytopenia
- Severe disease of liver, kidneys and pancreas.

Disease where there is a suspicious of vascular damage, e.g.

- Ulcer in the gastro-intestinal tract.
- Hypertension with diastolic blood pressure higher than 105mm Hg
- Intracranial haemorrhage
- Injuries or surgical procedures on the central nervous system.
- Cerebral arterial aneurysm
- Retinopathies , bleeding into the vitreum
- Ophthalmic surgical procedures
- Infectious endocarditis.

Imminent abortion
Spinal or epidural anaesthesia, lumbar puncture

As this preparations contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

Warning and Precautions
Warnings
Administration of Heparin Injection BP 1000 I.U. /ml and 5000 I.U/ml should normally be avoided in the following conditions, unless their expected benefits clearly outweigh possible risks:

- Suspected malignant tumour with risk of bleeding.
- Nephro-and ureterolithiasis
- Chronic alcohol abuse.

Especially careful medical monitoring is required:

- During pregnancy, esp. if heparin is to be administered over prolonged periods,
- In elderly patients,especially elderly women,
- During medication with fibrinolytics, ora anticoagulants, durg inhibiting platelet aggregation, such as acetylsalicyclic acid, ticlopidin, clopidogrel and/or glycoprotein – Iib/IIIa receptor blockers,
- Inpatients receiving medicaments that raise the serum potassium level.

In general, serum potassium levels should be monitored in patients at risk of hyperkalemia (e.g. due to diabetes mellitus, impaired renal function, or medicinal products that raise the serum potassium level).

During therapy with heparin, i.m injections must be avoided because of the risk of haematoma.
If thrombo-embolic complication occurs during therapy with heparin, type II heparin-induced thrombocytopenia must be considered and platelet count should be performed.

If heparin is administered to infants, children and patients with hepatic or renal failure, close monitoring including checks of the coagulation status is mandatory. This also applies to the use of heparin for prophylaxis of thrombo-embolism (low-dose therapy)

Patients under heparin therapy (more than 22 500 I.U./day) should not be exposed to the risk of injuries.

Heparin may lead to an increase and prolongation of menorrhagia. In case of unusual strong or acyclic uterine bleeding, any organic disease requiring specific treatment should be excluded by a supplementary gynecological examination.

Precautions

Heparin therapy must always be accompanied by regular controls of aPTT and platelet counts. Prior to administering heparin, the partial thromboplastin time and thrombin time should be determined. Their values should be within the normal range.

In order to detect the occurrence of a type II heparin-induced thrombocytopenia as early as possible, platelet counts should be performed

- Before the beginning of the therapy with heparin,
- On the 1st day of therapy,
- Every 3rd or 4th day during the first three weeks of therapy, and
- At the end of the therapy.

Heparin may cause various laboratory tests to yield incorrect results, such as erythrocyte sedimentation rate, erythrocyte resistance and complement binding tests.

Heparin may affect the prothrombin time; this should be considered when determining the dosage of coumarin derivatives.

Influence of heparin on laboratory tests:
Heparin may cause various laboratory tests to yields incorrect results, such as erythrocyte sedimentation rate, erythrocyte resistance and complement binding tests.
Under heparin therapy thyroid function tests may yield incorrect results, e.g. falsely high value of T_3 and T_4 levels.

This product contains animal part (porcine/pig)

Interaction with Other Medicaments

Other medicinal products
Enhancement of the Heparin Effect
Clinical significant enhancement of the heparin effect possibly associated with an increased tendency to bleeding may be brought about by:

- Platelet aggregation inhibitors such as acetylsalicyclic acid, ticlopidin, clopidogrel, dipyridamol at high doses,
- Fibrinolytics,
- Other anticoagulants (coumarin derivatives),
- Non-steroidal anti-inflammatory drug (phenylbutazone, indometacine, sulfinpyrazone),
- Glycoprotein –Iib/IIa receptor blockers,
- High-dose penicillin,
- Cytostatic drugs, except doxorubicin
- Dextrans

Weakening of the heparin effect
The heparin effect may be weakened by

- Doxorubicin
- Intravenous glyceryl trinitrate (nitro-glycerine)

After discontinuation of glycerol trinitrate the aPTT may rise suddenly. Heparin is administered during nitro-glycerine infusion, close monitoring the aPTT and adjustment of the heparin dose are necessary.

Inhibition of the heparin effect

The effect of heparin may be inhibited by:

- Ascorbic Acid
- Antihistamines,
- Digitalis (cardiac glycosides)
- Tetracyclins

Influence of Heparin on the effect of the other drug substances:

- Other drug substances being bound to plasma proteins (e.g propranolol):

Heparin may displace these from protein binding, leading to an enhancement of their effect.

- Drugs that lead to an increase of the serum potassium level: should only be administered together with heparin under careful monitoring.
- Alkaline drug substances (tricyclic psychotropic agents, antihistamines, or quinine): Heparin forms salt with these, leading to mutual weakening of their effects.

Other interactions

- Nicotine abuse:

Inhibition of the heparin effect is possible.

Incompatibilities

Heparin solutions should not be mixed with other drugs in a syringe or in an infusion solution because of possible physic-chemical incompatibilities.

Pregnancy and Lactation

Pregnancy

Heparin does not cross the placenta barrier. Until now there are no reports indicating development of foetal malformation due to heparin administration during pregnancy, nor are the finding from animal experiments indicating embryotoxic or foetotoxic effects of heparin.
An increased risk of accidental abortions and stillbirths, however, has been reported.
During pregnancy complications resulting from underlying illness and/or treatment cannot be excluded.
Daily administration of high heparin doses over more than 3 months may increase the risk of osteoporosis in pregnant women. Continuous administration of high doses of heparin should therefore not exceed 3 months.
Epidural anaesthesia must not be performed in obstetrics in pregnant women receiving anticoagulants.

Anticoagulation therapy is contraindicated in conditions characterised by an increase tendency to bleeding, such an imminent abortion.

Lactation

Heparin is not secreted into breast milk. Daily administration of high heparin does over more than 3 months may increase the risk of osteoporosis in breast-feeding women.

Side Effects

General
The most frequent but in most cases not serious undesirable effects are local reactions at the site of administration.
Besides this, bleeding complication may occur.
Heparin-induced thrombocytopenia of type II occur rarely but this adverse reaction may become serious. It is assumed to be hypersensitivity reaction mediated by specific antibodies. Details see below.
Other undesirable effects may include local or systemic allergic reactions.

Blood and lymphatic system disorders
Very Common
Depending on the dose, increased incidence of bleeding e.g. bleeding from skin, mucous membrane, wounds in the gastro-intestinal tract, the urinary tract and the genital tract. Bleeding complications may also affects organs e.g. brain and lungs.

Common
At the beginning of heparin therapy mild heparin-induced thrombocytopenia not mediated by antibodies (platelet count 100 000 – 150 000 per microliter) without thrombosis.

Immune system disorders
Uncommon
Systemic allergic reactions including nausea, headache, rise of temperature, limb pain, urticarial, vomiting, pruritus, dyspnea, bronchospasm and drop of blood pressure, local and general hypersensitivity reactions such as angioedema.

Rare
- Toxic or anaphylactoid reaction to benzyl alcohol.
- Severe heparin-induced, antibody-mediated thrombocytopenia (type II thrombocytopenia).

Very rare
- Anaphylactic shock especially in sensitized patients having previously received heparin.

- Onset of type II thrombocytopenia with delay of up to several weeks after the end of heparin administration.

Endocrine disorders
Rare
Hypoaldosteronism, resulting in hyperkalemia and metabolic acidosis, especially in patients with impaired kidney function and diabetes mellitus.

Vascular Disorders
Very rare
Vasospasm

Hepato-biliary disorders
Very Common
Increase of the serum concentration of transaminase (GOT, GPT), gamma-glutamyl transpeptidase, lactate dehydrogenase and lipase, which are however reversible and of no clinical significance.

Skin and subcutaneous tissue disorders
Uncommon:
Transient alopecia, skin necrosis.

Reproductive system and breast disorders
Very Rare
Priapism

General disorders and administration site conditions
Common
Local tissue reactions at the injection site, such as induration, redness, discoloration, and minor haematomas.

Very Rare
Calcinosis at the site of injection, mainly in patients with severe renal failure.

Information on particular undesirable effects
Severe heparin-induced, antibody-mediated thrombocytopenia (type II thrombocytopenia), is characterized by platelet counts markedly below 100 000 per microliter or a rapid decrease to less than 50% of the initial value and accompanied by arterial or venous thrombosis or embolism , consumption coagulopathy, skin necroses at the site of injection, pinpoint bleeding (petechia) and tarry stools (melaena). The actioagulatory effect of heparin may be reduced.

In patients without pre-existing hypersensitivity to heparin the decrease of the platelet count typically begins between 6 to 14 days after commencement of the heparin therapy. In patients with existing hypersensitivity to heparin such decrease may begin already after a few hours.
As soon as type II thrombocytopenia occurs, heparin administration must be discontinued immediately. Emergency treatment depends on the nature and severity of the symptoms. Re-exposure of the patient to parental heparin is absolutely contraindicated.

Symptoms and Treatment of Overdose
Bleeding in most cases from the skin, mucous membranes, wounds, in the gastro-intestinal tracts, the urinary tract and the genital tract (e.g. epistaxis, haematuria, melaena, haematomas, pinpoint bleeding). Drop of blood pressure, decrease of the haematocrit or other symptoms may indicate concealed bleeding.

Treatment
Mild Bleeding:
Can be stopped by simply reducing the dose.
Moderate, not life-threatening bleeding:
Heparin should be discontinued.

Severe life-threatening bleeding:
After exclusion of other causes such as deficiency of coagulation factors or consumption coagulopathy) administration of protamine to abolish the heparin effect.
Protamine should be given with great caution and for life-threatening haemorrhage only, because complete neutralisation of heparin will be associated with an increased risk of thrombosis. Further treatment should be under ICU conditions and include close monitoring of the patients.
Protamine is a protein rich of arginine, which is most commonly used in the form of its chloride or sulphate. As a rule, 1 mg of protamine will neutralise 100 I.U of heparin. The serum half life time and the route of administration pf heparin should be considered.

Thus,

- 90 min after intravenous administration of heparin, only half of the calculated amount of protamine should be given,
- 3 hours after heparin administration, only 25% of the calculated protamine dose.

Over titration with protamine may activate fibrinolysis and thus itself cause an increased tendency to bleeding. Too rapid i.v injection of protamine may cause dorp of blood pressure, bradycardia, dyspnoea, and sensation of discomfort. Protamine is eliminated from the circulation more rapidly than heparin. The efficacy of neutralisation is to be controlled by determinations of thrombin time and aPTT.

Heparin is not dialysable.

Storage Condition
Heparin Injection BP should be store at a temperature not exceeding 30^0C. Protect from light.

Shelf Life

i. Shelf life in the product as packaged for sale: 36 months
ii. Shelf life after first opening the container: Use immediately.
iii. Shelf life after dilution: Use immediately.

Presentation
Sterile solution for Injection in 5 mL USP type I clear glass Vial.

Manufactured by:
Gland Pharma Limited
Survey No. 143-148, 150 & 151
Near Gandimaisamma Cross Road,
D.P. Pally, Dundigal Post, Quthbullapur Mandal,
Ranga Reddy District, Hyderabad – 500 043,
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Product Registration Holder:

UNIMED SDN BHD

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