Heparin LEO injection

Anticoagulant

Vials
Heparin sodium 1,000 i.u., 5,000 i.u. or 25,000 i.u./ml, preservative: Benzyl alcohol, Methylparahydroxybenzoate, Propylparahydroxybenzoate.

Ampoules
Heparin sodium 1,000 i.u., 5,000 i.u., 10,000 i.u. or 25,000 i.u., without preservative.

Properties
Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in vivo and in vitro. Following administration of full therapeutic doses of heparin the wholeblood clotting time, the thrombin time and the one-stage prothrombin time are prolonged. The prolongation of clotting time is proportional to the dose administered. Whereas with therapeutic doses, the bleeding time is usually unaffected. In most cases the clotting time is not measurably affected by low doses of heparin.
Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can prevent the development of a hypercoagulable state by inactivating activated Factor X, preventing the conversion of prothrombin to thrombin (the principle of low dose prohylaxis). Once a hypercoagulable state exists, larger amounts of heparin in combination with antithrombin III can inhibit the coagulation process by inactivating thrombin and earlier clotting intermediates, thus preventing the conversion of fibrinogen to fibrin (the principle of full dose therapy). Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.
Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.
Menstruation and pregnancy are not contraindications to heparin therapy. Heparin does not cross the placenta or appear in breast milk.
In addition to the anticoagulant properties, heparin also has some lipaemia clearing effect, which may be utilized in the treatment and prevention of atherosclerosis and fat embolism.

Indications
Heparin is indicated for prophylaxis and treatment of venous thrombosis and pulmonary embolism; in the treatment of myocardial infarction and arterial embolism; for prevention of clotting in arterial and heart surgery and for prevention of cerebral thrombosis. Heparin may also be used as an anticoagulant in blood transfusions, extra-corporal circulation, dialysis procedures, and for laboratory purposes.

Administration
Heparin is usually administered by intravenous or subcutaneous injection. The intramuscular route cannot be recommended because of the high incidence of haematoma.
The increase in clotting time provided by heparin becomes apparent immediately after administration and lasts for 4 to 6 hours after intravenous injection and for about eight hours after subcutaneous injection.

Dosage
Haemodialysis: 7,500–12,500 i.u. (without preservative) is normally required per dialysis. Intravenous administration: 5,000–10,000 i.u. every four hours either by bolus injection or continuous infusion in Sodium Chloride Injection or Dextrose Injection. However, the dose should be monitored with coagulation tests performed just before each administration and varied according to individual response. The clotting time should be 2–3 times the control value.
Subcutaneous administration (Therapeutic dosage): Subcutaneous administration of 10,000 i.u. may be given every 8 hours after an initial intravenous bolus injection of 5,000 i.u.
Low-dose heparin prophylaxis: 5,000 i.u. in 0.2 ml s.c. should be given two to six hours pre-operatively and every 8–12 hours post-operatively for 10–14 days, or until the patient is mobile, whichever is the longer.
Myocardial infarction: 5,000 i.u. s.c. every twelve hours beginning during the twelve hours following the first sign of myocardial infarction.
Open heart surgery: Operations of less than two hours, 120 i.u./kg/hour. For operations of longer duration, one and a half times this dose should be given. For each 450 ml of blood used, 2,000 i.u. are needed.
Treatment periods vary from 10–14 days in peri-operative prophylaxis to as much as six weeks in the treatment of established thrombosis.
It is anticipated that heparin will have disappeared from the blood-stream 4 hours after intravenous injection of 5,000 i.u. and 6–8 hours after 10,000 i.u. and 15,000 i.u. of i.v. heparin, respectively.
In situations needing large amounts of heparin, as in cardio-pulmonary bypass, preservative-free heparin should be used. If this is unavailable and preserved heparin has to be used, then the most concentrated heparin solution (25,000 IU/ml) should be chosen to minimise the quantity of preservative administered.

Pregnancy
The antithrombotic drug of choice during pregnancy should be heparin, even taking into consideration the fact that longterm (6 months or more) application of heparin can cause severe osteoporosis in the mother. To minimize the risk of osteoporosis heparin is given in the first trimester, followed by coumarin therapy until about the 36th week, and then heparin is given for the last few weeks. Heparin therapy should be completely stopped six hours before delivery.

Contraindications
Heparin is contraindicated in patients known to have hypersensitivity to heparin. It is also contraindicated when suitable blood coagulation tests – e.g. the whole-blood clotting time, partial thromboplastin time, – cannot be performed at the required intervals. There is usually no need to monitor the effect of low-dose heparin in patients with normal coagulation parameters. The drug is contraindicated during any uncontrolled active bleeding state (see Warnings).
Heparin without preservatives should be used in premature infants.

Side-effects
Transient alopecia and diarrhoea may occur. Thrombocytopenia and osteoporosis with spontaneous fractures have been reported. Febrile or allergic reactions have occasionally been reported.

Warnings
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 haemorrhage occurs heparin sodium should be discontinued promptly (See Overdosage).
Some of the conditions in which increased danger of haemorrhage exists are as follows:
Cardiovascular – Subacute bacterial endocarditis; arterial sclerosis; increased capillary permeability; during and immediately following (a) spinal tap or spinal anaesthesia or (b) major surgery, especially involving the brain, spinal cord or eye.
Haematologic – Conditions associated with increased bleeding tendencies, such as haemophilia, some purpuras, and thrombocytopenia.
Gastro-intestinal – Inaccessible ulcerative lesions and continuous tube drainage of the stomach or small intestine.
Heparin may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least five 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.

Overdosage
Bleeding may be a complication of therapy.
Slight epistaxis, occasional red cells in the urine, and bruising are signs of overdosage.
Slight haemorrhage due to overdosage can usually be treated by withdrawing the drug. Severe bleeding may be reduced by the administration of protamine sulphate.
The effect of heparin can be reversed immediately by intravenous administration of 1% protamine sulphate solution. The injection should be given very slowly (over one to three minutes). The quantity of protamine required for neutralization falls rapidly with the lapse of time after the adminstration of heparin. If given within 15 minutes of the heparin injection 10 mg of protamine will neutralize 1,000 i.u. of heparin, while 30 minutes after the heparin injection of 1,000 i.u., only 5 mg of protamine sulphate is needed. If more time has elapsed after the administration of heparin, the dose of protamine sulphate required for neutralization should be determined accurately by titrating with the patient's plasma.
It is important to avoid overdosage of protamine sulphate because protamine itself has anticoagulant properties. The dosage should not exceed the equivalent of 50 mg protamine sulphate in any ten-minute period. Intravenous injection of protamine may cause a sudden fall in blood pressure, bradycardia, dyspnoea, and transitory flushing, but these may be avoided or diminished by slow administration.

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Storage Conditions
Store at controlled room temperature (15°C-25°C)

Precautions
Heparin therapy should be given with caution to patients about to undergo surgery, and those with impaired renal or hepatic function.
If oral anticoagulants are started, heparin should be continued in slightly decreasing doses for another 4–5 days until the oral drug has attained full prothrombin depressing activity.
Heparin should be used with caution in any patient with a history of allergy. Before a therapeutic dose is given to such a patient, a trial dose of 1,000 units may be advisable.

Dosage in the elderly
Elderly women have a greater tendency to bleed and it may be necessary to reduce the dose according to coagulation tests, but dosage alterations are unlikely for prophylaxis.

Interactions
Drugs (such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, and hydroxychloroquine) that interfere with platelet-aggregation reactions may induce bleeding and should be used with caution in patients receiving heparin. It may be necessary to increase doses of heparin in the febrile state.
Digitalis, tetracycline, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium. An increased resistance to the drug is frequently encountered in thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, and postsurgical patients.

Package sizes: 5,000 IU/ml: 5 ml x 50, 5 ml x 5
1,000 IU/ml: 5 ml x 50, 5 ml x 5

Shelf life
3 years

Date of last revision of the package insert leaflet: 23 August 2011.

LEO Pharmaceutical Products - Ballerup - Denmark

THIS IS A MEDICAMENT

- Medicament is a product, but not like other products.
- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the Doctor s prescription, the method of use and the instructions of the pharmacist who sold you the medicament. The Doctor and Pharmacist are experts in medicaments, their benefits and their risks.
- Do not by yourself interrupt the period of treatment prescribed to you.
- Do not repeat the same medicament and do not increase doses without consulting your Doctor.

Do not leave medicament within reach of children

Council of Arab Health Ministers – Union of Arab Pharmacists.

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