PACKAGE INSERT

HEPALEAN®

Heparin Sodium Injection U.S.P.
Anticoagulant
Porcine intestinal mucosa origin.
Schering-Plough Canada Inc., Kirkland, Québec H9H 4M7

DESCRIPTION

HEPALEAN® (heparin sodium injection) is a sterile, pyrogen-free solution of a highly purified sodium salt of heparin, a high molecular weight polysaccharide derived from porcine intestinal mucosa. It is standardized in vitro according to the method of U.S.P. and is labelled in terms of U.S.P. units for use as an anticoagulant. It acts very rapidly and, even in large doses, is metabolized in the body and eliminated within 24 hours. It will not lyse existing thrombi or emboli.

HEPALEAN®, being of intestinal mucosal origin, offers two advantages over that derived from lung tissue, namely, the potency of U.S.P. units per unit weight is higher and the amount of protamine sulfate required for neutralization of the heparin is much less.

ACTIONS

Heparin sodium inhibits the clotting of blood and the formation of fibrin clots both in vitro and in vivo. In combination with a cofactor, it inactivates thrombin thus 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.

Heparin sodium inhibits reactions which lead to clotting but does not alter the normal components of the blood. Although clotting time is prolonged by therapeutic doses, bleeding time is usually unaffected. Heparin sodium does not have fibrinolytic activity; therefore, it will not lyse existing clots.

INDICATIONS

Used in the treatment of thrombophlebitis, phlebothrombosis, and cerebral, coronary, and retinal vessel thrombosis to prevent extension of clots and thromboembolic phenomena.

Also used prophylactically to prevent the occurrence of thromboembolism, and to prevent clotting during dialysis and surgical procedures, particularly vascular surgery.

When using HEPALEAN®(heparin sodium injection) in conjunction with dialysis machines or where the HEPALEAN® is added to glucose or saline it is most important that the pH is not less than 5 for HEPALEAN® to act as an effective anticoagulant. Under pH 5 degradation sets in and with a pH around 4 or less there is very little HEPALEAN® activity. Likewise with pH over 8.5 there will be some degradation. Recent work has indicated that early hemodialysis is of value in cases of multiple trauma.

HEPALEAN® has also been used as an anticoagulant in blood transfusion samples, particularly when the presence of citrates, oxalates or fluorides might interfere with laboratory tests, such as electrolyte determination. Anti-inflammatory and diuretic activity have been obtained with HEPALEAN®, however, these properties have not yet been put to any widespread clinical use.

Low-dose Subcutaneous Heparin:

For the prevention of serious venous thromboembolic complications in high risk surgical patients.

CONTRAINDICATIONS

Hemophilia and severe clotting disorders; shock; hypersensitivity to heparin; severe liver damage.

Active bleeding from a local lesion such as an acute ulcer or ulcerating carcinoma. Recent neurosurgery or spinal surgery.

WARNINGS

1. Administration of large doses of HEPALEAN® (heparin sodium injection) should be delayed four hours postoperatively.

2. When any of the conditions mentioned under precautions are present the advantages of HEPALEAN® therapy must be carefully weighed against the possibility of deleterious results.

PRECAUTIONS AND INCOMPATABILITIES

Precautions:
Purpura, and other blood dyscrasias with bleeding tendencies; active ulcerative diseases of the gastrointestinal tract; jaundice; subacute bacterial endocarditis; increased capillary fragility; threatened abortion; postoperative disease, following brain or spinal cord surgery.
Malignant hypertension: HEPALEAN® (heparin sodium injection) should be used with caution in the immediate postoperative period. Bleeding may be concealed, as in the case of hemothorax.

HEPALEAN® should be used with caution in pregnancy although this does not cross the placental barrier and is the safest and most useful form of therapy in thromboebolic disorders of pregnancy.

For these reasons strict laboratory control of dosage is necessary. HEPALEAN® should be used with caution in patients with allergy. Patients on long term daily administration of HEPALEAN® should be observed for the possible development of osteoporosis and spontaneous fractures of ribs and /or vertebrae.

Care must be taken where large doses of antibiotics and/or drugs containing amino groups are administered along with or prior to HEPALEAN® administration.

Drugs such as codeine phosphate, pethidine hydrochloride, streptomycin, erythromycin, kanamycin, neomycin, novobiocin, tetracyclines, ampicillin, penicillin G, polymyxin B, vancomycin, hydrocortisone sodium succinate, pentobarbitone, promazine hydrochloride, vitamin B complex, vitamin C may complex with HEPALEAN® - this complex may be reversible (heparin rebound) and may result in excess bleeding at the surgical site. Extra protamine sulfate may then be indicated.

Please also refer to the pH requirements in hemodialysis under INDICATIONS.

Incompatabilities:

Heparin has not been reported to interact pharmacologically in vivo with any other drugs. An increased bleeding tendency may be seen when heparin is used in combination with ethacrynic acid, aspirin and dextran. Although digitalis, quinine, tetracycline, antihistamines, and nicotine have been stated to interfere with the anticoagulant activity of heparin, there is no substantial literature support for such interactions. The chemical interaction occurring between heparin and protamine is well known. This interaction is used clinically to antagonize the anticoagulant effect of heparin.

Ethacrynic Acid - Intravenously administered ethacrynic acid can cause GI bleeding. However, a significantly higher incidence of GI bleeding has been attributed to the concurrent use of intravenous ethacrynic acid and heparin. Furosemide may be a safer alternative when such diuretic therapy is indicated in the patient receiving heparin.

Aspirin - In a review article of heparin therapy, it was advocated that concurrent aspirin administration be scrupulously avoided. While documentation to support this interaction is incomplete, it would be prudent to avoid concurrent therapy. Aspirin impairs the platelet release reaction and this platelet function defect combined with the anticoagulant effect of heparin may produce a hemorrhagic tendency.

Dextran - Limited data suggest that dextran and heparin may act synergistically when administered concurrently. Although the data are inadequate to document the clinical significance of this interaction, baseline laboratory measurements of anticoagulant activity should be obtained upon initiation of concurrent therapy as well as at frequent intervals during such therapy.

ADVERSE EFFECTS

Hemorrhage is the chief complication which may develop during HEPALEAN® (heparin sodium injection) therapy. Please refer to the section entitled “HEPARIN NEUTRALIZATION WITH PROTAMINE”.

Hypersensitivity reactions, such as fever, skin eruptions, nasopharyngeal congestion, bronchial asthma, anaphylactic shock, and osteoporosis, have been reported in some patients following HEPALEAN® injection. Alopecia, affecting the entire scalp or confined to the temple, has been reported with the use of HEPALEAN®; the mechanism is unknown.

Thrombocytopenia has also been described with heparin treatment. Heparin Induced Thrombocytopenia (HIT) is an allergic reaction. It has been reported to occur in 1 to 30% of patients treated with standard heparin. It has also occurred with the use of LMWHs, both in patients with a history of HIT and patients with no previous exposure to heparin. The risk of developing HIT may be lower with LMWHs, but cannot be reliably estimated until more patients have been exposed. It is thought to be more common with heparin derived from bovine lung (5 - 10%) than from porcine gut (2 - 5%). Two types of acute, reversible thrombocytopenia have been described. Mild thrombocytopenia most commonly occurs between 5 and 12 days after initiation fo full dose therapy. Platelet count usually remains above 100 x 109/L, and heparin therapy does not necessarily have to be withdrawn. Platelet count may remain stable or even increase despite continued therapy; however, it should still be monitored. The more severe, delayed form of thrombocytopenia (platelets <100 x 109/L), is much less frequent, usually appearing 5 to 12 days after starting heparin therapy and recurs rapidly on rechallenge. It has occurred with low dosages and is not dose related. It is generally reversible, platelet counts usually begin to return to normal within 4 days of stopping heparin. Paradoxically, patients may develop thrombotic complications including arterial thrombosis, gangrene, stroke, myocardial infarction and disseminated intravascular coagulation. Thrombosis is due to “white clots” composed of platelets and fibrin that result from marked in vivo platelet aggregation. Patients receiving heparin acutely should have platelet counts monitored at least every 2 or 3 days.

Heparin Neutralization With Protamine

Bleeding which may occur during therapy with heparin sodium can usually be corrected by withdrawal. Clotting time should then return to normal in 30 to 60 minutes provided venous clotting time is not longer than 15 minutes when the infusion is interrupted. Should withdrawal of heparin sodium fail to control bleeding, fresh, matched blood (not more than three days old) may be administered in quantities of 250 to 500ml.

The most rapid means of counteracting the effects of heparin is intravenous administration of protamine sulfate injection. However, protamine sulfate is by itself an anticoagulant and therefore excess must be avoided. The amount of heparin sodium neutralized by protamine sulfate varies with the organ from which it is derived, method of manufacture and specific activity of heparin sodium. The amount of protamine sulfate required to neutralize 1,000 units of each lot of heparin sodium used in the preparation of HEPALEAN® is therefore accurately determined and is stated on the label as the number of milligrams of protamine sulfate required to neutralize 1,000 units of HEPALEAN®.

Allowance should be made for the rapid removal of heparin sodium from circulation. The rate of heparin sodium removal from plasma is dose-dependent. However, it may be assumed that about 30 minutes after an intravenous injection, about 50% of the heparin sodium is removed from circulation.

So the amount of protamine sulfate required to neutralize the heparin sodium will be approximately half of that required for the original dose. For example if 1,000 units required 8.4 mg of protamine sulfate for neutralization, half an hour after intravenous administration of a 5,000 unit dose, the amount of protamine sulfate required will only be approximately

5/2x8.4 = 21mg

Do not administer more than 50 mg protamine sulfate at any one time.

DOSAGE AND ADMINISTRATION

PLEASE NOTE:

1. Intramuscular injection (especially in the arm or thigh) and shallow subcutaneous injection is not recommended. The duration of effect is shortened and it is more likely to produce pain and hematoma.

2. Heparin sodium activity is expressed in U.S.P. units and should be prescribed in units only.

The route of administration may be I.V. or S.C. depending upon the situation and the choice of the prescriber. Adequate heparin-induced anticoagulant therapy is present when the clotting time is elevated from 2 to 3 times normal as measured by the Lee-White method. Two types of dosage schedules are suggested: HEPALEAN® (heparin sodium injection) may be administered intravenously in a dose of 5,000 U.S.P. units every 4 hours or in a dose of 10,000 U.S.P. units every 6 hours, depending upon the results of a whole blood clotting time test performed at the bedside just prior to each additional dose. If the clotting time is less than twice normal, the next dose is increased by one-third to one-half. If the clotting time is more than 2-1/2 times normal, the next dose is decreased by one-third to one-half. If the clotting time is between 2 and 2-1/2 times normal, the regular dose is repeated.

SUBCUTANEOUS INJECTION TECHNIQUE:

Use of a 1 ml tuberculin syringe with a No. 25 or No. 26 -1/2 inch needle is recommended.

STEP 1. Disinfect area with alcohol then apply pressure between finger and thumb to the dermal fold until the injection site is blanched.

STEP 2. Insert the needle into the raised, blanched area. Reduce the pressure on the skin and inject the HEPALEAN® slowly.

STEP 3. Withdraw the needle quickly and apply alcohol swab with pressure to the site of injection for 5-10 seconds to prevent loss of the heparin.

DOSAGE

Administration		RECOMMENDED DOSAGE*
Method	**FREQUENCY**	
Low-dose Subcutaneous†	**Every 8-12 hours**	**5,000 units**
Subcutaneous	**Every 8 hours**	**10,000 to 20,000 units initially ** then 8,000 to 10,000 units three times a day.**
Intermittent Intravenous	**Every 4 to 6 hours**	**10,000 units initially, then 5,000 to 10,000 units four to six times a day**
Intravenous Infusion	**Continuous or Intermittent**	**20,000 to 40,000 units per litre at a rate of 15 to 30 units per minute.**
Dialysis	**See below**	**See below**
Usual Pediatric Dose	**Every 4 hours**	**By intravenous infusion, 50 units per kg of body weight initially, followed by 100 units per kg or 3,333 units per square meter of body surface, six times a day.**

*based on 68 kg of body weight (approx. 150 lbs.)

† It is not necessary to monitor low-dose prophylactic HEPALEAN®

**Following immediately after an initial dose of 5,000 units I.V.

THERAPY REQUIRED:

1. Low Dose Subcutaneous Heparin Sodium

   There is now good evidence that low dose heparin sodium is effective in preventing serious venous thromboembolic complications in high risk surgical patients. The usually recommended dose is 5,000 units given subcutaneously 2 hours before surgery and then 5,000 units given either 12 hourly or 8 hourly after surgery with the first dose given at approximately 12 hours after surgery. It is not necessary to monitor low dose prophylactic heparin.

2. Therapeutic Anticoagulant Action (immediate and short term).

   The dose should be adjusted in keeping with the patient's clotting time which should be determined just prior to the injection during the first day of treatment. It is also recommended that, in order to help regulate dosage, the clotting time be determined on the second and third day of treatment. (The recommended method is the Lee-White whole blood method.)

   Anticoagulation is adequate when the clotting time is 2 to 3 times the normal value.

   Subcutaneous administration is usually employed for maintenance therapy after initial regulation.

3. Long Term Protective Anticoagulant Action

   Subcutaneous administration of 15, 000 units every 12 hours is usually employed. Daily injections of 20,000 to 30,000 units have also been employed with success. After initial regulation the dosage should be adjusted according to weekly to monthly clotting time determinations. Anticoagulant therapy should not be terminated abruptly but should be gradually reduced over 3-4 days.

4. Deep Venous Thrombosis and Pulmonary Embolism

   Dosage of 20,000 units daily for 6-10 days has been of value.

5. Hemodialysis

   (a) Multiple Trauma

   Recent literature has suggested the use of early hemodialysis in multiple trauma.

   (b) Chronic Renal Failure

   The use of hemodialysis in this area has increased dramatically in recent years and may be in-hospital or home dialysis.

It is most important to stress that the instructions for each manufacturer's equipment unit must be followed scrupulously.

The following is merely intended as an overall summary of possible general procedures:

3,000 units of HEPALEAN® (heparin sodium injection) is added to 1,000 ml of sterile saline as a dialyser flush prior to connection.

Initial dosage: 5,000 units of HEPALEAN® into the venous shunt or 2,500 units into the arterial fistula needle.

With the shunt type the usual continuing dosage is 2,000 units per hour; with the fistula type - 1,500 units per hour by means of suitable syringe and a pump to allow continuing infusion. HEPALEAN® reversal with protamine sulfate will be decided by the individual physician. Usually this is not done unless dialysis is being performed soon after surgery.

6. Coronary and Vascular Surgery

Patients undergoing total body perfusion for open heart surgery should receive an initial dose of not less than 150 units of HEPALEAN® per kilogram of body weight. Frequently a dose of 300 units of HEPALEAN® per kilogram of body weight is used for procedures estimated to last less than 60 minutes; or 400 units/kg for those estimated to last longer than 60 minutes.

SUPPLY

HEPALEAN® (heparin sodium injection) is supplied in the following concentrations and package sizes. Please note that all HEPALEAN® injections are colour-coded.

Strength	Package Size
1,000 units/ml (Black Label)	30 ml vial
	10ml vial
	1 ml vial*
10,000 units/ml (Red Label)	5ml vial
	1ml vial*
25,000 units/ml (Blue Label)	2ml vial

*Each 1 mL (single use) vial also contains: sodium chloride, hydrochloric acid and/or sodium hydroxide,
Each multi use vial also contains: sodium chloride, benzyl alcohol (as preservative), hydrochloric acid and/or sodium hydroxide,

All vials are supplied in cartons of 10.
*All 1 ml vials are supplied in cartons of 100.