PRESCRIBING INFORMATION

Heparin Sodium Injection, USP

1000 USP Units / mL, 10 000 USP Units / mL vials
5000 USP Units / 0.5 mL Prefilled Syringe

Sterile Solution

For Intravenous or Subcutaneous Use

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Heparin Sodium Injection, USP

Anticoagulant

DESCRIPTION

Heparin Sodium Injection, USP is a sterile, non-pyrogenic 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 USP and is labeled in terms of USP 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.

ACTIONS

Heparin 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 Heparin Sodium Injection, USP in conjunction with dialysis machines or where the Heparin Sodium Injection, USP is added to glucose or saline, it is most important that the pH is not less than 5 for heparin sodium to act as an effective anticoagulant. Under pH 5, degradation sets in and with a pH around 4 or less, there is very little heparin sodium 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.

Heparin sodium injection 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 has been obtained with heparin sodium injection; 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

Patients with a generalized clotting disorder such as hemophilia, Christmas disease, idiopathic thrombocytopenic purpura and patients with active bleeding from a local lesion such as an acute ulcer or ulcerating carcinoma; patients who have had recent cranial, spinal, eye or ear surgery or trauma; hypersensitivity to heparin, including thrombocytopenia; severe liver damage; shock.

WARNINGS

1. Administration of large doses of Heparin Sodium Injection, USP should be delayed 4 hours postoperatively.

2. When any of the conditions mentioned under PRECAUTIONS are present, the advantages of Heparin Sodium Injection, USP therapy must be carefully weighed against the possibility of deleterious results.

PRECAUTIONS

The use of intravenous heparin in the treatment of ischemic stroke is controversial. Clinical trials investigating the benefits of heparin in ischemic stroke have been inconclusive. Heparin may increase the risk of clinically significant cerebral bleeding. Administration of an intravenous bolus of heparin is not recommended in the treatment of stroke. If heparin is used, brain imaging should be performed prior to initiation of therapy to exclude hemorrhage and estimate infarct size.

When considered for use in any of the following conditions, the advantages of heparin therapy must be carefully weighed against the risks: subacute bacterial endocarditis; increased capillary permeability; dissecting aneurysm; severe hypertension; during and immediately following major surgery, especially of the brain, spinal cord, eye or ear; conditions associated with increased bleeding tendencies such as hemophilia, thrombocytopenia and some purpuras;

inaccessible gastrointestinal ulcers; ulcerative colitis; continuous tube drainage of stomach or small intestine; threatened abortion; menstruation; malignant hypertension.

Heparin Sodium Injection, USP should be used with caution in the immediate postoperative period. Bleeding may be concealed, as in the case of hemothorax.

In patients with a history of heparin-induced thrombocytopenia (HIT), heparinoids (e.g., danaparoid), lepirudin and ancrod are considered appropriate alternatives to heparin.

When used in therapeutic doses, heparin should be regulated by frequent blood coagulation indicators, particularly the APTT. If the indicator is unduly prolonged or if hemorrhage occurs, heparin should be at least temporarily discontinued (see OVERDOSAGE).

Heparin can prolong the prothrombin time.

Apparent resistance to heparin may be encountered in patients with acquired or familial AT III deficiency, because adequate levels of AT III are required for heparin's anticoagulant effect. Larger doses of heparin may be required initially in patients with various disease states due to alterations in their physiology, the pharmacokinetics of the drug, or elevations in levels of acute phase heparin binding proteins. Among these are febrile illness, infections associated with thrombosing tendencies, pulmonary embolism, myocardial infarction, extensive thrombotic disorders especially those associated with neoplastic disease and following surgery.

Heparin should be used with caution in the presence of severe hepatic or renal disease, or in patients with indwelling catheters. A higher incidence of bleeding may be seen in women over 60 years of age.

Intramuscular injections of other drugs should be avoided during heparin therapy to reduce the risk of hematoma formation and bleeding from the site. Most drugs can be given by another route (intravenous or subcutaneous).

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

Drug Interactions

Oral anticoagulants (i.e., warfarin) can contribute to a small extent to an increase in APTT. Heparin can contribute to an increase in PT. While these two drugs are given together, the fact that each may contribute to an increase in PT and APTT should be taken into account (see PRECAUTIONS).

Heparin is often started with or several hours after thrombolytic therapy. Close patient monitoring for clinical signs of bleeding is indicated. The APTT should also be monitored closely (see DOSAGE AND ADMINISTRATION).

Salicylates, other nonsteroidal anti-inflammatory agents, dextran, dipyridamole, clopidogrel, ticlopidine and GPIIb-IIIa antagonists (e.g., abciximab) interfere with platelet aggregation which

increases the risk of bleeding. They should be used cautiously with monitoring for signs of hemorrhage. In addition, in some situations, when heparin is used in conjunction with GPIIb-IIIa antagonists, the dose of heparin may need to be modified (see DOSAGE AND ADMINISTRATION, THERAPY REQUIRED, Coronary and Vascular Surgery).

Cefamandole, cefotetan, methimazole, propylthiouracil and valproic acid may cause hypoprothrombinemia and increase the risk of bleeding; monitoring for signs of bleeding is indicated. This may occur to a lesser extent with cefazolin, cefoxitin and ceftriaxone.

Intravenous nitroglycerin may reduce heparin's anticoagulant effect and necessitate higher doses. This interaction has been reported to occur regardless of whether or not propylene glycol is used as a solvent for the nitroglycerin. The mechanism has not been conclusively documented. When intravenous nitroglycerin therapy is initiated, patients should be closely monitored to ensure anticoagulation remains adequate. Likewise, when nitroglycerin therapy is stopped, a decrease in heparin dosage may be necessary and patients should be monitored for signs of excessive anticoagulation.

Digitalis, quinine, ACTH, insulin, corticosteroids, antihistamines and nicotine have been reported to interfere with the anticoagulant effect of heparin; however, there is no substantial literature support to document these interactions.

Care must be taken where large doses of antibiotics and/or drugs containing amino groups are administered along with or prior to Heparin Sodium Injection, USP administration. Drugs such as codeine phosphate, pethidine hydrochloride, streptomycin, erythromycin, kanamycin, neomycin, novobiocin, tetracyclines, ampicillin, penicillin G, polymyxin B, vancomycin, hydrocortisone sodium succinate (S-Cortilean), pentobarbitone, promazine hydrochloride, vitamin B complex, vitamin C.

Heparin sodium may complex with these drugs -- this complex may be reversible (heparin rebound) and may result in excess bleeding at the surgical site. Extra protamine sulfate may then be indicated.

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 anti-coagulant 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 diuretic therapy is indicated in the patient receiving heparin.

Acetylsalicylic Acid
In a review article of heparin therapy, it was advocated that concurrent acetylsalicylic acid administration be "scrupulously avoided". While documentation to support this interaction is incomplete, it would be prudent to avoid concurrent therapy. Acetylsalicylic acid 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.

Pregnancy
Heparin does not cross the placenta and has not been related to congenital defects. However, its use during pregnancy has been associated with a 13 to 22% risk of fetal mortality or prematurity. It is not clear whether severity of maternal disease or an indirect effect of heparin is responsible. Coumarin anticoagulants have been associated with a 31% incidence of unfavourable outcome and a definite drug-induced pattern of malformations has been demonstrated (fetal warfarin syndrome). However, the incidence of warfarin-induced fetopathic effects in the second and third trimesters is very low. In general, heparin is considered to be the anticoagulant of choice in pregnancy. Long-term usage (> 3 to 5 months) of therapeutic doses of heparin during pregnancy increases the risk of osteoporosis and warrants careful monitoring of patients. Heparin therapy during the last trimester and immediate postpartum period is associated with a risk of maternal hemorrhage. Changes in pharmacokinetics during pregnancy require caution and close patient monitoring if heparin is used.

Reports of therapeutic failure with adjusted-dose heparin therapy in pregnant patients with prosthetic heart valves may have been due to inadequate dosing and/or monitoring, or to an inherent lack of efficacy in these patients. The American College of Chest Physicians recommends that if subcutaneous heparin is used in pregnant patients with mechanical heart valves, it be administered every 12 hours and the dose adjusted to keep the mid-interval APTT at least twice the control, or an anti-Xa heparin level of 0.35 to 0.7 U/mL. In addition, some clinicians suggest an initial dose of 17 500 to 20 000 units subcutaneous every 12 hours.

Lactation
Heparin is not excreted in breast milk because of its high molecular weight.

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

ADVERSE EFFECTS

Bone and Joint: Therapeutic doses of heparin administered for longer than 3 months have been associated with osteoporosis and spontaneous vertebral fractures. Recent reports indicate that osteoporosis may be reversible after discontinuation of heparin.

Hematologic: Bleeding is the most common side effect of heparin and is an extension of its pharmacological effect. The rate of occurrence is approximately 10% overall but may increase up to 20% in patients treated with high-dose therapy. Risk of bleeding likely increases with

APTT ratios above the recommended target range. Other risk factors associated with bleeding are: a serious concurrent illness, chronic heavy consumption of alcohol, use of platelet-inhibiting drugs, renal failure, age and female sex. Bleeding may range from minor local ecchymoses to major hemorrhagic events. Often the first sign of bleeding may be epistaxis, hematuria or melena. Bleeding may be from any site and can be difficult to detect, e.g., retroperitoneal bleeds. Bleeding may also occur from surgical sites. Petechiae or easy bruising may precede frank hemorrhage. A supratherapeutic APTT or minor bleeding during therapy can usually be controlled by adjusting the dosage or withdrawing the drug (see OVERDOSAGE).

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 of full dose therapy. Platelet count usually remains above 100 x 10^9/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 10^9/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.

Hepatic: Heparin has been reported to cause elevations of AST and ALT in approximately 27 and 59% of patients, respectively. Transient increases in serum LDH levels have also occurred. No clinical signs of liver dysfunction have been reported and the significance is not known, except that interpretation of liver enzymes for other purposes (i.e., liver disease) must take into consideration the possible contribution of heparin.

Hypersensitivity: Heparin-induced thrombocytopenia (see ADVERSE EFFECTS, Hematologic). Other allergic reactions to heparin are rare. The most common manifestations of hypersensitivity are chills, fever and urticaria. Asthma, rhinitis, tearing, headache, nausea, vomiting, shock and anaphylactoid reactions have also occurred. Vasospasm has been reported 6 to 10 days after starting heparin; the etiology is thought to be allergic. Vasospasm often appears in a limb where an artery has recently been catheterized. The affected limb is usually painful, ischemic and cyanotic. Protamine sulfate is of no use in hypersensitivity reactions.

Miscellaneous: Alopecia, affecting the entire scalp or confined to the temple, may occur. Itching and burning of the plantar surfaces of the feet, suppression of aldosterone product, hyperkalemia (due to aldosterone suppression), priapism and rebound hyperlipidemia have also been reported.

Heparin Neutralization with Protamine

Bleeding which may occur during therapy with heparin 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 500 mL.

The most rapid means of counteracting the effects of heparin is intravenous administration of protamine sulfate injection. However, protamine is by itself an anticoagulant and therefore excess must be avoided. **A dosing ratio of 1 milligram protamine for every 100 units of heparin remaining in the patient is the usual rule.** It is recommended that protamine doses be guided by blood coagulation studies to determine if additional doses are required. The activated partial thromboplastin time (APTT) or activated clotting time (ACT) are adequate for this purpose.

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

So the amount of protamine sulfate required to neutralize the heparin will be that of approximately half of that required for the original dose. For example, if 1000 units required 10 mg of protamine sulfate for neutralization, half an hour after intravenous administration of a 5000 unit dose, the amount of protamine sulfate required will only be approximately:

$$5 / 2 \times 10 = 25 \text{ mg}$$

Too rapid administration of protamine can cause severe hypotensive and anaphylactoid reactions. Facilities to treat shock should be readily available when administering protamine. The rate of protamine administration should not exceed 20 mg/min and no more than 50 mg should be given in any 10-minute period. Doses exceeding 100 mg in a short period of time should be avoided, unless there is certain knowledge of larger protamine requirements. Any excess protamine sulfate, not complexed to heparin, has its own intrinsic anticoagulant effect. However, one study found overdose of protamine up to 600 to 800 mg intravenous to have only minor, transient effects on blood coagulation.

OVERDOSAGE

Symptoms: Overdose may be manifested by excessive prolongation of the APTT or by bleeding. Bleeding may be internal or external, major or minor.

Treatment: See ADVERSE EFFECTS, Heparin Neutralization with Protamine.

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 USP units and should be prescribed in units only.

The route of administration may be intravenous or subcutaneous, 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 schedule are suggested: Heparin Sodium Injection, USP may be administered intravenously in a dose of 5000 USP units every 4 hours or in a dose of 10 000 USP 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 2½ times normal, the next dose is decreased by one-third to one-half. If the clotting time is between 2 and 2½ times normal, the regular dose is repeated.

SUBCUTANEOUS INJECTION TECHNIQUE

Use of a 1 mL tuberculin syringe with a No. 25 or No. 26 - ½ 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 Heparin Sodium Injection, USP slowly.

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

DOSAGE

ADMINISTRATION		
METHOD	**FREQUENCY**	**RECOMMENDED DOSAGE***
Low-dose Subcutaneous†	Every 8 to 12 hours	5000 units
Subcutaneous	Every 8 hours	10 000 to 20 000 units initially** then 8000 to 10 000 units three times a day.
Intermittent Intravenous	Every 4 to 6 hours	10 000 units initially, then 5000 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 3333 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 Heparin Sodium Injection, USP.

** Following immediately after an initial dose of 5 000 units intravenous

DILUTION INSTRUCTIONS FOR INTRAVENOUS INFUSION

Heparin Sodium Injection, USP may be diluted to 20 000 to 40 000 units per litre (or 20 units to 40 units / mL) with 5% Dextrose Injection; 0.9% Sodium Chloride Injection; 0.45% Sodium Chloride Injection; 5% Dextrose and 0.45% Sodium Chloride Injection; or 5% Dextrose and 0.9% Sodium Chloride Injection in PVC bag. Diluted solution may be stored up to 24 hours at controlled room temperature.

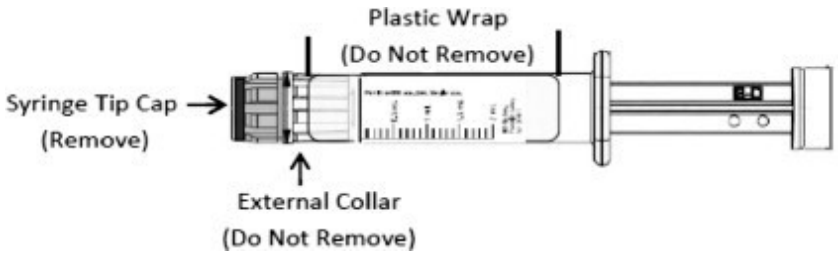
As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

INSTRUCTIONS FOR USE - PREFILLED SYRINGE

CAUTION: Certain glass syringes may malfunction, break or clog when connected to some Needleless Luer Access Devices (NLADs) and needles. This syringe has a larger internal syringe tip and an external collar (luer collar). The external collar must remain attached to the syringe. Data show that the syringe achieves acceptable connections with the BD Eclipse™ Needle and the Terumo SurGuard2™ Safety Needle and with the following non-center post NLADs: Alaris SMARTSITE™, B-Braun ULTRASITE™, BD-Q SYTE™, and B-Braun SAFSITE™. The data also show acceptable connections are achieved to the center post ICU Medical CLAVE™. However, spontaneous disconnection of this glass syringe from needles and NLADs with leakage of drug product may occur. Assure that the needle or NLAD is securely attached before beginning the injection. Visually inspect the glass syringe-needle or glass syringe –NLAD

connection before and during drug administration. Do not remove the clear plastic wrap around the external collar (see Figure 1).

Figure 1



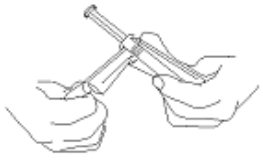
1. Inspect the outer packaging (blister pack) by verifying:
   - blister integrity
   - drug name
   - drug strength
   - dose volume
   - route of administration
   - expiration date to be sure that the drug has not expired
   - sterile field applicability

   Do not use if package has been damaged.

2. Peel open the paper (top web) of the outer packaging that displays the product information to access the syringe. Do not pop syringe through.

3. Bend the plastic part of the outer packaging (thermoform) so as to present the plunger rod for syringe removal (see Figure 2).

Figure 2



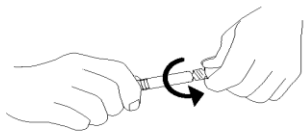
4. Perform visual inspection on the syringe by verifying
   - Absence of syringe damage
   - Absence of external particles
   - Absence of internal particles
   - Proper drug colour

- Expiration date to be sure that the drug has not expired
- Drug name
- Drug strength
- Dose volume
- Route of administration
- Sterile field applicability
- Integrity of the plastic wrap around the external collar

5. Do not remove plastic wrap around the external collar. Push plunger rod slightly to break the stopper loose while tip cap is still on.

6. Do not remove plastic wrap around the external collar. Remove tip cap by twisting it off (see Figure 3).

Figure 3



7. Discard the tip cap.

8. Expel air bubble.

9. Adjust dose into sterile material (if applicable).

10. Connect the syringe to appropriate injection connection depending on route of administration. Before injection, ensure that the syringe is securely attached to the needle or needleless luer access device (NLAD).

11. Depress plunger rod to deliver medication. Ensure that pressure is maintained on the plunger rod during the entire administration.

12. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle. If delivering the medication with a needle, to prevent needle stick injuries, do not recap needle.

NOTES:
- All steps must be done sequentially.
- **Do not autoclave syringe.**
- **Do not use this product on a sterile field.**
- Do not introduce any other fluid into the syringe at any time.
- This product is for single use only

THERAPY REQUIRED

1. Low-dose Subcutaneous Heparin Sodium

There is now good evidence that low-dose heparin is effective in preventing serious venous thromboembolic complications in high-risk surgical patients. The usually recommended dose is 5000 units subcutaneously 2 hours before surgery and then 5000 units given every 12 or 8 hours 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 to 4 days.

4. Deep Venous Thrombosis and Pulmonary Embolism

Dosage of 20 000 units daily for 6 to 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 equipment manufacturer's unit must be followed scrupulously.

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

- 3000 units of Heparin Sodium Injection, USP is added to 1000 mL of sterile saline as a dialyser flush prior to connection.
- Initial dosage: 5000 units of Heparin Sodium Injection, USP into the venous shunt or 2500 units into the arterial fistula needle.
- With the shunt type, the usual continuing dosage is 2000 units per hour; with the fistula type, 1500 units per hour by means of a suitable syringe and a pump to allow continuing infusion. Heparin Sodium Injection, USP 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 Heparin Sodium Injection, USP per kilogram of body weight. Frequently a dose of 300 units of Heparin Sodium Injection, USP 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.

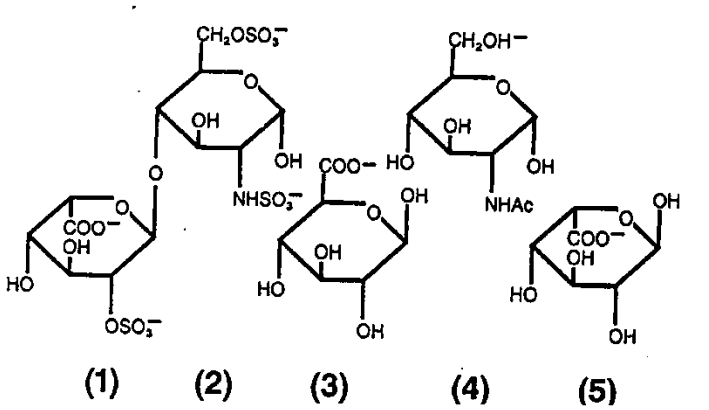
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Heparin Sodium

CAS No.: 9041-08-1

Structural Formula:



Description: Heparin is a heterogeneous group of straight-chain anionic mucopolysaccarides, called glycosaminoglycans, having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions. Heparin sodium is derived from porcine intestinal mucosa, standardized for anticoagulant activity.

STABILITY AND STORAGE RECOMMENDATIONS

Store Heparin Sodium Injection, USP vial at 15 °C to 30 °C. Protect from freezing. For multidose vials, discard unused portion 28 days after initial puncture. For single use vials, discard unused portion.

Store Heparin Sodium Injection, USP prefilled syringe at 15 °C to 30 °C. Protect from freezing. Single use prefilled syringe. Discard unused portion**. Do not place syringe on a sterile field.**

AVAILABILITY OF DOSAGE FORMS

Heparin Sodium Injection, USP is supplied in the following concentrations and package sizes. **Vial stoppers do not contain natural rubber latex.**

C504701 Heparin 1000 USP Units / mL, 1 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, sodium chloride 9 mg / mL for isotonicity, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504710 Heparin 1000 USP Units / mL, 10 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, sodium chloride 9 mg / mL for isotonicity, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504730 Heparin 1000 USP Units / mL, 30 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, sodium chloride 9 mg / mL for isotonicity, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504801 Heparin 10 000 USP Units / mL, 1 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504805 Heparin 10 000 USP Units / mL, 5 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504301 Heparin 10 000 USP Units / mL, 0.5 mL fill in 2 mL single use vial in package of 25 vials. Preservative free. Also contains Water for Injection q.s. Porcine intestinal mucosa origin.

C504013 Heparin 1000 USP Units / mL, 1 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, sodium chloride 9 mg / mL for isotonicity, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504015 Heparin 1000 USP Units / mL, 10 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, sodium chloride 9 mg / mL for isotonicity, Water for Injection q.s. Porcine intestinal mucosa origin.

C504036 Heparin 1000 USP Units / mL, 30 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, sodium chloride 9 mg / mL for isotonicity, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504213 Heparin 10 000 USP Units / mL, 1 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504214 Heparin 10 000 USP Units / mL, 5 mL fill in multidose vial in package of 25 vials. Also contains methylparaben 1.5 mg / mL, propylparaben 0.15 mg / mL, and Water for Injection q.s. Porcine intestinal mucosa origin.

C504313 Heparin 10 000 USP Units / mL, 0.5 mL fill in single use vial in package of 25 vials. Preservative free. Also contains Water for Injection q.s. Porcine intestinal mucosa origin.

CS761805 Heparin 5000 USP Units / 0.5 mL fill in 1.25 mL Simplist™ prefilled single use syringes, in a carton of 24 prefilled syringes. Preservative free. Also contains sodium chloride 5 mg / mL for isotonicity and Water for Injection q.s. Porcine intestinal mucosa origin. Ready to administer.

Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to use.

This prescribing Information is prepared by:

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