

ARTWORK DETAILS

Division : Ancard
 Brand Name : Caprin
 Dimension : L: 139 mm x H: 215 mm
 Pack Size : 5 ml
 Artwork No : 21863

Insert Type : Insert
 Board :
 GSM :
 Lamination :
 Location : Unit II

COLOR DETAILS

Pantone Solid Coated



K: 100

or minor bleeding during therapy can usually be controlled by withdrawing the drug. It should be appreciated that gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:

(a) Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since delay in an acute situation may result in the patient's death.

(b) Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short- or long-term anticoagulant therapy. This complication, if unrecognized, may be fatal.

(c) Retroperitoneal hemorrhage.

Local Irritation

Local irritation, erythema, mild pain, hematoma or ulceration may follow deep subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.

Hypersensitivity

Generalized hypersensitivity reactions have been reported, with chills, fever and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar site of the feet, may occur. Thrombocytopenia has been reported to occur in patients receiving heparin sodium with a reported incidence of 0 to 30%. While often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possibly death. Certain episodes of painful, ischemic and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia-associated complications remains to be determined.

Miscellaneous

Osteoporosis following long-term administration of high-doses of heparin sodium, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, pruritus and rebound hyperlipemia on discontinuation of heparin sodium have also been reported. Significant evaluations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin sodium.

OVERDOSE:

Symptoms

Bleeding is the chief sign of heparin sodium overdose. Nosebleeds, blood in urine or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Treatment

Neutralization of Heparin Effect: When clinical circumstances (bleeding) require reversal of heparinization, protamine sulfate (1% solution) by slow infusion will neutralize heparin sodium. No more than 50 mg should be administered, very slowly, in any 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 USP Heparin Units. The amount of protamine required decreases over time as heparin is metabolized. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about 1/2 hour after intravenous injection. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

DRUG INTERACTIONS:

a. Drugs Enhancing Heparin Effect:

Oral anticoagulants: Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 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.

Platelet inhibitors: Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. Thus in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with antithrombin III (human).

b. Drugs Decreasing Heparin Effect:

Digitalis, tetraacyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium. Heparin Sodium Injection should not be mixed with doxorubicin, droperidol, ciprofloxacin, or mitoxantrone, since it has been reported that these drugs are incompatible with heparin and a precipitate may form.

STORAGE:

Store at a temperature not exceeding 30°C.

PRESENTATION:

Caprin 5000IU - 10 vials of Caprin (Heparin Injection BP 5000IU/5ml) in a box.
 Caprin 25000IU - 10 vials of Caprin (Heparin Injection BP 25000IU/5ml) in a box.

Manufactured by:



UNIT II, Plot No. 2, Industrial Area, Lodhimagra, Baddi, H.P. - 173 205, India.
 H.O.: Ram Mandir Road, Goregaon (W), Mumbai - 400 104, India.
 Registered Trade Mark of Samarth

21863

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.



Heparin Injection BP

5000 IU/5 ml
 25000 IU/5 ml

For IV/SC use only



Composition:

Each ml contains:
 Heparin Sodium BP 1000 IU
 (Derived from Porcine Intestinal Mucosa)
 Benzyl Alcohol BP 1% v/v
 (As preservative)
 Water for Injections BP q.s.

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DESCRIPTION:

Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, having anticoagulant properties.

CLINICAL PHARMACOLOGY:

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 antithrombin 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. Loglinear plots of heparin plasma concentrations with time, for a wide range of dose levels, are linear, which suggests the absence of zero order processes. Liver and the reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase (t_{1/2} = 10 min), and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin. Patients over 60 years of age, following similar doses of heparin, may have higher plasma levels of heparin and longer activated partial thromboplastin times (APTTs) compared with patients under 60 years of age. Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

THERAPEUTIC INDICATIONS:

CAPRIN is indicated for anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension (in a low-regimen); for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominal thoracic surgery or who, for other reasons, are at risk of developing thromboembolic disease for prophylaxis and treatment of pulmonary embolism, for atrial fibrillation with embolization; for diagnosis and treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation); for prevention of clotting in arterial and heart surgery; for prophylaxis and treatment of peripheral arterial embolism; as an anticoagulant in blood transfusion, extracorporeal circulation and dialysis procedures, and in blood samples for laboratory purposes.

DOSAGE & ADMINISTRATION:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency. When heparin sodium is added to an infusion solution for continuous intravenous administration, the container should be inverted at least six times to insure adequate mixing and prevent pooling of the heparin sodium in the solution.

Heparin sodium is not effective by oral administration and should be given by intermittent intravenous injection, intravenous infusion or deep subcutaneous (intrafat, i.e., above the iliac crest or abdominal fat layer) injection. **The intramuscular route of administration should be avoided because of the frequent occurrence of hematoma at the injection site.**

The dosage of heparin sodium should be adjusted according to the patient's coagulation test results. When heparin sodium is given by continuous intravenous infusion, the coagulation time should be determined approximately every four hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection coagulation tests should be performed before each injection during the early stages of treatment and at appropriate intervals thereafter. Dosage is considered adequate when the activated partial thromboplastin time (APTT) is 1.5 to 2 times normal or when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value. After deep subcutaneous (intrafat) injections tests for adequacy of dosage are best performed on samples drawn four to six hours after the injections.

Periodic platelet counts, hematocrits and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

Heparin Sodium Injection should not be mixed with doxorubicin, droperidol, ciprofloxacin, or mitoxantrone, since it has been reported that these drugs are incompatible with heparin and a precipitate may form.

SIGN & DATE

R. A.

Q. A.

Q. C.

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THERAPEUTIC ANTICOAGULANT EFFECT WITH FULL-DOSE HEPARIN
 Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage schedules may be used as guidelines:

METHOD OF ADMINISTRATION	FREQUENCY	RECOMMENDED DOSE*
Deep Subcutaneous (Intrafat) Injection	Initial Dose	5,000 Units by IV injection followed by 10,000 to 20,000 Units of a concentrated solution, subcutaneously
	Every 8 hours	8,000 to 10,000 Units of a concentrated solution
	Every 12 hours	15,000 to 20,000 Units of a concentrated solution
A different site should be used for each injection to prevent the development of massive hematoma		
Intermittent Intravenous Injection	Initial Dose	10,000 Units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, USP
	Every 4 to 6 hours	5,000 to 10,000 Units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, USP
	Continuous	5,000 Units by IV injection
Continuous Intravenous Infusion	Initial Dose	20,000 to 40,000 Units/24 hours in 1,000 mL of 0.9% Sodium Chloride Injection USP (or in any compatible solution for infusion)
	Continuous	

* Based on 150 lb. (68 kg) patient.

Pediatric Use

Follow recommendations of appropriate pediatric reference texts. In general, the following dosage schedule may be used as a guideline:

Initial Dose:	50 units/kg (I.V., drip)
Maintenance Dose:	100 units/kg (I.V., drip) every four hours, or 20,000 units/m ² /24 hours continuously

Geriatric Use

Patients over 60 years of age may require lower doses of heparin.

Surgery of the Heart and Blood Vessels

Patients undergoing total body perfusion for open-heart surgery should receive an initial dose of not less than 150 Units of heparin sodium per kilogram of body weight. Frequently, a dose of 300 Units per kilogram is used for procedures estimated to last less than 60 minutes or 400 Units per kilogram for those estimated to last longer than 60 minutes.

Low-Dose Prophylaxis of Postoperative Thromboembolism

A number of well-controlled clinical trials have demonstrated that low-dose heparin sodium. Prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep vein thrombosis in the legs (as measured by the 1-125 fibrinogen technique and venography) and of clinical pulmonary embolism. The most widely used dosage has been 5,000 Units two hours before surgery and 5,000 Units every 8 to 12 hours thereafter for seven days or until the patient is fully ambulatory, whichever is longer. The heparin sodium is given by deep subcutaneous (intrafat, i.e., above the iliac crest or abdominal fat layer, arm or thigh) injection with a fine (25 to 26 gauge) needle to minimize tissue trauma. A concentrated solution of heparin sodium is recommended. Such prophylaxis should be reserved for patients over the age of 40 who are undergoing major surgery. Patients with bleeding disorders and those having brain or spinal cord surgery, spinal anesthesia, eye surgery or potentially sanguineous operations should be excluded, as should patients receiving oral anticoagulants or platelet-active drugs.

The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or postoperatively should be borne in mind. If such bleeding occurs, discontinuance of heparin sodium and neutralization with protamine sulfate are advisable. If clinical evidence of thromboembolism develops despite low-dose prophylaxis, full therapeutic doses of anti-coagulants should be given unless contraindicated. Prior to initiating heparinization the physician should rule out bleeding disorders by appropriate history and laboratory tests, and appropriate coagulation tests should be repeated just prior to surgery. Coagulation test values should be normal or only slightly elevated at these times.

Extracorporeal Dialysis

Follow equipment manufacturers' operating directions carefully.

Blood Transfusion

Addition of 400 to 600 USP Units per 100 mL of whole blood is usually employed to prevent coagulation. Usually, 7,500 USP Units of heparin sodium are added to 100 mL of 0.9% Sodium Chloride Injection, USP (or 75,000 USP Units/1000 mL of 0.9% Sodium Chloride Injection, USP) and mixed; from this sterile solution, 6 to 8 mL is added per 100 mL of whole blood.

CONTRAINDICATIONS:

Heparin sodium should not be used in patients:

- With severe thrombocytopenia.

- In whom suitable blood coagulation tests e.g. the whole-blood clotting time, partial thromboplastin time, etc. cannot be performed at appropriate intervals (this contraindication refers to full-dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low-dose heparin sodium).
- With an uncontrollable active bleeding state, except when this is due to disseminated intravascular coagulation.

WARNINGS:
 Heparin sodium is not intended for intramuscular use.

Hypersensitivity

Patients with documented hypersensitivity to heparin sodium should be given the drug only in clearly life-threatening situations.

Hemorrhage

Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a hemorrhagic event. Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

Cardiovascular: Subacute bacterial endocarditis, severe hypertension

Surgical: During and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord or eye.

Hematologic: Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia, and some vascular purpuras.

The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. Thus in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with antithrombin III (human).

Gastrointestinal: Ulcerative lesions and continuous tube drainage of the stomach or small intestine.

Other: Menstruation, liver disease with impaired hemostasis.

Coagulation Testing

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 hemorrhage occurs, heparin sodium should be discontinued promptly.

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving heparin sodium with a reported incidence of 0 to 30%. 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, the heparin sodium product should be discontinued. If continued heparin sodium therapy is essential, administration of heparin from a different organ source can be reinstated with caution.

Miscellaneous

This product contains benzyl alcohol as preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

PRECAUTIONS:

General

a. White Clot Syndrome: It has been reported that patients on heparin sodium may develop new thrombus formation in association with thrombocytopenia, resulting from irreversible aggregation of platelets induced by heparin the so-called "white clot syndrome." The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possibly death. There, heparin sodium administration should promptly be discontinued if a patient develops new thrombosis in association with thrombocytopenia.

b. Heparin Resistance: Increased resistance to heparin sodium is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

c. Increased Risk in Older Women: A higher incidence of bleeding has been reported in women over 60 years of age.

Laboratory Tests

Periodic platelet counts, hematocrits and tests for occult blood in stool are recommended during the entire course of heparin sodium therapy, regardless of the route of administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin sodium. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects: Heparin sodium does not cross the placental barrier.

Nursing Mothers

Heparin is not excreted in human milk.

Pediatric Use

See **DOSAGE AND ADMINISTRATION.**

Geriatric Use

A higher incidence of bleeding has been reported in patients over 60 years of age, especially women.

ADVERSE EFFECTS:

Hemorrhage

Hemorrhage is the chief complication that may result from heparin sodium therapy. An overly prolonged clotting time

SIGN & DATE

R. A.

Q. A.

Q. C.