CAPRIN
(Heparin Injection BP 5000IU/5ml)

1.4.1 Prescribing Information

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:
CAPRIN (Heparin Injection BP 5000 IU/5ml)

1.1 Strength:
5000 IU/ 5ml

1.2 Pharmaceutical form:
Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch Size: 200 Liter

Sr. No.	Name of Ingredient	Specification	Qty per ml	Overages added	Qty per Batch	Uses
1.	Heparin Sodium (Derived from porcine intestinal mucosa)	BP	1000 IU	--	1.0816 kg	Active Ingredient (Anticoagulant)
2	Benzyl Alcohol	BP	1% v/v	--	2 Liters	Preservative
3.	Water for Injection	BP	q.s.	--	200.0 Liters	Vehicle

Note : Quantity varies as per potency of raw material.

q.s. - Quantity Sufficient

3. PHARMACEUTICAL FORM:

Injection

Product Description : Clear colourless solution filled in a 5ml clear glass vial, labeled, stoppered and sealed with green coloured flip-off seal, such ten vials along with packing insert is packed in a carton.

4. CLINICAL PARTICULARS

4.1. Therapeutic indication(s)

It is an anticoagulant indicated for:

Prophylaxis and treatment of venous thromboembolism.

Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation.

Treatment of acute and chronic consumption coagulopathies.

Prevention of clotting in arterial and cardiac surgery.

Prophylaxis and treatment of peripheral arterial embolism.

Anticoagulant use in transfusion, extracorporeal circulation, and dialysis procedures.

4.2 Posology and method of administration

Adults

For Intermittent intravenous, Infusion intravenous and Subcutaneous.

Recommended Adult Full-Dose Heparin Regimens for Therapeutic Anticoagulant Effect

Method of Administration	Frequency	Recommended Dose
Deep Subcutaneous (Intrafat) Injection Use a different site for each injection to prevent the development of hematoma	Initial Dose Every 12 hours	333 units/kg subcutaneously 250 units/kg subcutaneously
Intermittent Intravenous Injection	Initial Dose	10,000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, 5,000 to 10,000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection,
	Every 4 to 6 hours	
Continuous Intravenous Infusion	Initial Dose Continuous	5,000 units by IV injection 20,000 to 40,000 units per 24 hours in 1,000 mL of 0.9% Sodium Chloride Injection, (or in any compatible solution) for infusion

* Based on 150 lb (68 kg) patient.

Pediatric Use

Initial Dose Maintenance	75 to 100 units/kg (IV bolus over 10 minutes) Infants: 25 to 30 units/kg/hour;
Dose	Infants < 2 months have the highest requirements (average 28 units/kg/hour) Children > 1 year of age: 18 to 20 units/kg/hour; Older children may require less heparin, similar to weight-adjusted adult dosage
Monitoring	Adjust heparin to maintain a PTT of 60 to 85 seconds, assuming this reflects an anti-Factor Xa level of 0.35 to 0.70.

Cardiovascular Surgery: 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: The most widely used dosage has been 5,000 units 2 hours before surgery and 5,000 units every 8 to 12 hours thereafter for 7 days or until the patient is fully ambulatory, whichever is longer. Administer the heparin 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.

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, (or 75,000 USP units per 1,000 mL of 0.9% Sodium Chloride Injection,) and mixed; from this sterile solution, 6 to 8 mL are added per 100 mL of whole blood.

4.3 Contraindications:

It is contraindicated in patients as;

History of heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis.

Known hypersensitivity to heparin or pork products (e.g., anaphylactoid reactions).

In whom suitable blood coagulation tests (e.g., whole-blood clotting time, partial thromboplastin time) cannot be performed at appropriate intervals.

4.4 Special warnings and precautions for use:

Heparin is not intended for intramuscular use.

Hypersensitivity

Patients with documented hypersensitivity to heparin 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 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, reduction in platelet count of any degree should be monitored closely. If the count falls below 100,000/mm3 or if recurrent thrombosis develops the heparin product should be discontinued.

Precaution:

White Clot Syndrome

It has been reported that patients on heparin 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. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with a reduction in platelet count.

Heparin Resistance

Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, in postsurgical patients, and patients with antithrombin III deficiency.

Increased Risk to older Patients, Especially Women

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

Pediatric population :

Initial Dose	75 to 100 units/kg (IV bolus over 10 minutes)
Maintenance Dose	Infants: 25 to 30 units/kg/hour; Infants < 2 months have the highest requirements (average 28 units/kg/hour) Children > 1 year of age: 18 to 20 units/kg/hour; Older children may require less heparin, similar to weight-adjusted adult dosage
Monitoring	Adjust heparin to maintain a PTT of 60 to 85 seconds, assuming this reflects an anti-Factor Xa level of 0.35 to 0.70.

4.5 Interaction with other medicinal products and other forms of interaction

The anticoagulant effect of heparin may be enhanced by concomitant medication with other drugs affecting platelet function or the coagulation system, e.g. platelet aggregation inhibitors, thrombolytic agents, salicylates, non-steroidal anti-inflammatory drugs, vitamin K antagonists, dextrans, activated protein C. Where such combination cannot be avoided, careful clinical and biological monitoring is required.

Combined use with ACE inhibitors or angiotensin II antagonists may increase the risk of hyperkalaemia. Use of glyceryl trinitrate infusion may reduce the anticoagulant effect of heparin.

4.6 Fertility, pregnancy and lactation

Fertility: Not available

Pregnancy and lactation :

Heparin does not cross the placenta and therefore adverse effects to the fetus would not be expected. Heparin is considered safer to the fetus than warfarin when used during pregnancy.

Heparin has not been shown to cause birth defects or bleeding problems in the baby. However, use during the last three months of pregnancy or during the month following the baby's delivery may cause bleeding problems in the mother, and therefore monitoring is required.

The use of epidural anesthesia during labor, for women being medically treated for anticoagulation, is absolutely contraindicated.

Heparin does not pass into breast milk.

4.7 Effects on ability to drive and use machines:

Not available

4.8 Undesirable effects:

The following adverse reactions have been identified during post approval use are;

Hemorrhage: Hemorrhage is the chief complication that may result from heparin therapy . 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 including:

- Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred with heparin therapy, including fatal cases.
- Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short- or long-term heparin therapy.
- Retroperitoneal hemorrhage.

HIT and HITT, including delayed onset cases:

1. Local irritation – Local irritation, erythema, mild pain, hematoma, or ulceration have occurred following deep subcutaneous (intrafat) injection of heparin sodium. Because such reactions occur more frequently after intramuscular administration, the IM route is not recommended.

2. Histamine-like reactions – Such reactions have been observed at the site of injection. Necrosis of the skin has been reported at the site of subcutaneous injection of heparin, occasionally requiring skin grafting.

– Hypersensitivity – Generalized hypersensitivity reactions have been reported with chills, fever, and urticaria as the most usual manifestations; asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occur less frequently. Itching and burning, especially on the plantar site of the feet, may occur.

– Elevations of serum aminotransferases – Significant elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have occurred in patients who have received heparin.

Others – Osteoporosis following long-term administration of high doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipemia on discontinuation of heparin sodium have been reported.

4.13 Overdose

Bleeding is the chief sign of heparin overdosage.

Neutralization of Heparin Effect: When clinical circumstances (bleeding) require reversal of the heparin effect, 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 30 minutes after intravenous injection.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

ATC Code(s): B01AB01

Pharmacotherapeutic group: Pharmacotherapeutic group: Anticoagulant.

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.

5.2 Pharmacokinetic properties:

Peak plasma levels of heparin are achieved 2–4 hours following subcutaneous administration, although there are considerable individual variations. Log-linear 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 ($t_{½}$ = 10 minutes) and, after the age of 40 a slower beta phase, indicate 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.

5.3 Preclinical safety data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Benzyl Alcohol BP
Water for injection BP

6.2 Incompatibilities:

Heparin has been reported to be incompatible in aqueous solution with certain substances, e.g. some antibiotics, hydrocortisone, phenothiazines, narcotic analgesics and some antihistamines.

6.3 Shelf life:

24 months from the date of manufacture.

6.4 Special precautions for storage:

Store at a temperature not exceeding 30°C. .

6.5 Nature and contents of container:

Heparin Injection is available as a 10 x 5ml clear glass vial containing 5000 IU of Heparin sodium BP.

6.6 Special precautions for disposal and other handling:

Only clear solution free from particles and discolouration should be used.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS:

Samarth Life Sciences Pvt. Ltd.
Unit II, Plot No. 2, Industrial Area,
Lodhimajra, Baddi, Dist. Solan,
Himachal Pradesh – 173205, India.
Telephone: 09736036973
01795 – 220508

8. MARKETING AUTHORISATION NUMBERS

Not applicable

9. DATE OF FIRST REGISTRATION /RENEWAL OF THE REGISTRATION

Not applicable

10.DATE OF REVISION OF THE TEXT

Not applicable

11.DOSIMETRY (IF APPLICABLE)

Not applicable

12.INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable