CAPRIN
(Heparin Injection BP 25000IU/5ml)

1.4.1 Prescribing Information

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:
CAPRIN (Heparin Injection BP 25000 IU/5ml)

1.1 Strength:
25000 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	5000 IU	--	5.123 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

BP : British Pharmacopoea

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

Method of administration

By continuous intravenous infusion in 5% glucose or 0.9% sodium chloride or by intermittent intravenous injection, or by subcutaneous injection.

The intravenous injection volume of heparin injection should not exceed 15ml. As the effects of heparin are short-lived, administration by intravenous infusion or subcutaneous injection is preferable to intermittent intravenous injections.

Posology

Prophylaxis of deep vein thrombosis and pulmonary embolism.

Adults*:*

2 hours pre-operatively:	5,000 units subcutaneously
followed by:	5,000 units subcutaneously every 8-12 hours, for 7-10 days or until the patient are fully ambulant.

No laboratory monitoring should be necessary during low dose heparin prophylaxis. If monitoring is considered desirable, anti-Xa assays should be used as the activated partial thromboplastin time (APTT) is not significantly prolonged.

Elderly:

Dosage reduction and monitoring of APTT may be advisable.

Paediatric population: No dosage recommendations.

Treatment of deep vein thrombosis and pulmonary embolism:

Adults:

Loading dose:	5,000 units intravenously (10,000 units may be required in severe pulmonary embolism)
Maintenance:	1,000-2,000 units/hour by intravenous infusion, or 10,000-20,000 units 12 hourly subcutaneously, or 5,000-10,000 units 4-hourly by intravenous injection.

Elderly:

Dosage reduction may be advisable.

Children and small adults:

Loading dose:	50 units/kg intravenously
Maintenance:	15-25 units/kg/hour by intravenous infusion, or 250 units/kg 12 hourly subcutaneously, or 100 units/kg 4-hourly by intravenous injection.

Treatment of unstable angina pectoris and acute peripheral arterial occlusion:

Adults:

Loading dose:	5,000 units intravenously
Maintenance:	1,000-2,000 units/hour by intravenous infusion, or 5,000-10,000 units 4-hourly by intravenous injection.

Elderly:
Dosage reduction may be advisable.

Children and small adults:

Loading dose:	50 units/kg intravenously
Maintenance:	15-25 units/kg/hour by intravenous infusion, or 100 units/kg 4-hourly by intravenous injection.

Daily laboratory monitoring (ideally at the same time each day, starting 4-6 hours after initiation of treatment) is essential during full-dose heparin treatment, with adjustment of dosage to maintain an APTT value 1.5-2.5 x midpoint of normal range or control value.
Prophylaxis of mural thrombosis following myocardial infarction

Adults*:*
12,500 units 12 hourly subcutaneously for at least 10 days.

Elderly:
Dosage reduction may be advisable
In extracorporeal circulation and haemodialysis

Adults:
Cardiopulmonary bypass:
Initially 300 units/kg intravenously, adjusted thereafter to maintain the activated clotting time (ACT) in the range 400-500 seconds.
Haemodialysis and haemofiltration: Initially 1,000-5,000 units,
Maintenance: 1,000-2,000 units/hour, adjusted to maintain clotting time >40 minutes.

Heparin resistance
Patients with altered heparin responsiveness or heparin resistance may require disproportionately higher doses of heparin to achieve the desired effect. Also refer to section 4.4, Special warnings and precautions for use.

4.4 Contra-indications :

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1. This heparin formulation contains the preservative benzyl alcohol and so must not be given to children up to 3yrs old or neonates. As benzyl alcohol may cross the placenta the use of this formulation must be avoided in pregnancy.
Current (or history of) heparin-induced thrombocytopenia. Generalised or local haemorrhagic tendency.
An epidural anaesthesia during birth in pregnant women treated with heparin is contraindicated.
Regional anaesthesia in elective surgical procedures is contra-indicated because the use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis.

4.5 Special warnings and precautions for use :

Heparin should be used with caution in patients with hypersensitivity to low molecular weight heparin.

Care should be taken when heparin is administered to patients with increased risk of bleeding complications, hypertension, renal or hepatic insufficiency.

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

Drugs affecting platelet function, or the coagulation system should in general not be given concomitantly with heparin.

In patients undergoing peri-dural or spinal anaesthesia or spinal puncture, the prophylactic use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. The risk is increased by the use of a peri-dural or spinal catheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs, platelet inhibitors or anticoagulants and by traumatic or repeated puncture. In decision making on the interval between the last administration of heparin at prophylactic doses and the placement or removal of a peri-dural or spinal catheter, the product characteristics and the patient profile should be taken into account. Subsequent dose should not take place before at least four hours have elapsed. Re-administration should be delayed until the surgical procedure is completed.

Should a physician decide to administer anti-coagulation in the context of peridural or spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment, such as back pain, sensory and motor deficits and bowel or bladder dysfunction. Patients should be instructed to inform immediately a nurse or a clinician if they experience any of these.

Heparin should not be administered by intramuscular injection due to the risk of haematoma.

Due to increased bleeding risk, care should be taken when giving concomitant intramuscular injections, lumbar puncture and similar procedures.

As there is a risk of antibody-mediated heparin-induced thrombocytopenia, platelet counts should be measured in patients receiving heparin treatment for longer than 5 days and the treatment should be stopped immediately in those who develop thrombocytopenia.

Heparin induced thrombocytopenia and heparin induced thrombocytopenia with thrombosis can occur up to several weeks after discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for heparin induced thrombocytopenia and heparin induced thrombocytopenia with thrombosis.

Heparin Injection contains benzyl alcohol (10mg/ml) as preservatives. Caution should be used if prescribing Heparin Injection to susceptible patients. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to three years old.

4.7 Interaction with other medicinal products and other forms of interaction

Heparin may prolong the one stage prothrombin time. Accordingly, when Heparin is given with dicoumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose of heparin should elapse before blood is drawn, if a valid prothrombin time is to be obtained.

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.

4.8 Additional information on special populations : Not available

4.9 Pediatric population : Not available

4.10 Fertility, pregnancy and lactation

As benzyl alcohol may cross the placenta, the use of this formulation should be avoided during pregnancy.
The use of heparin in women with abortus imminens is contraindicated (see Section 4.3). Heparin does not cross the placental barrier and is not excreted in breast milk.

4.11 Effects on ability to drive and use machines :

There are no known effects on ability to drive and use machines.

4.12 Undesirable effects :

The following adverse reactions have been observed and reported during treatment with Heparin Sodium with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (<1/10 000), not known (cannot be estimated from available data).
Adverse Drug Reactions

System Organ Class (SOC)	MedDRA Preferred Term	Frequency
Vascular disorders	Haemorrhage	Not known
	Epistaxis	Not known
	Contusion	Not known
Blood and lymphatic system disorders	Thrombocytopenia	Not known
Renal and urinary disorders	Haematuria	Not known
Endocrine disorders	Adrenal insufficiency	Not known
	Hypoaldosteronism	Not known

Skin and subcutaneous tissue disorders	Alopecia	Not known
	Skin necrosis	Not known
Musculoskeletal, connective tissue and bone disorders	Osteoporosis	Not known
Immune system disorders	Hypersensitivity	Not known
Metabolism and nutrition disorders	Rebound hyperlipidaemia	Not known
	Hyperkalaemia Hypokalaemia	Not known
Reproductive system and breast disorders	Priapism	Not known
General disorders and administration site conditions	Injection site reaction	Not known
Investigations	Alanine aminotransferase increased; Aspartate aminotransferase increased	Not known

Erythematous nodules, or infiltrated and sometimes eczema-like plaques, at the site of subcutaneous injections are common, occurring 3-21 days after starting heparin treatment.

Haemorrhage:

Haemorrhage is the chief complication that may result from heparin therapy. An overly prolonged clotting time 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 haemorrhage complications may be difficult to detect.

Adrenal haemorrhage, 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 haemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.

4.13 Overdose:

Bleeding is the main sign of overdose with heparin**.**

As heparin is eliminated quickly, a discontinuation of treatment is sufficient in case of minor haemorrhages. In case of severe haemorrhages heparin may be neutralised with protamine sulphate injected slowly intravenously. One mg of protamine sulphate neutralises approximately 100 IU of heparin. Nevertheless, the required protamine sulphate dose varies according to the time of heparin administration and the dose administered.

It is important to avoid overdosage of protamine sulphate because protamine itself has anticoagulant properties. A single dose of protamine sulphate should never exceed 50 mg. 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 and careful administration

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

ATC Code(s): B01AB01

Pharmacotherapeutic group: Pharmacotherapeutic group: Anticoagulant.

Heparin prevents the coagulation of blood in-vivo and in-vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X.

5.2 Pharmacokinetic properties:

Absorption

Heparin is not absorbed from the gastrointestinal tract. Heparin is administered by injection.

Distribution

Heparin binds extensively to plasma proteins.

Elimination

Heparin and its metabolites are excreted in the urine.

The half-life of heparin depends on the dose administered, the route of administration and is subject to wide inter- and intraindividuavariation

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:

None

6.3 Shelf life:

24 months from the date of manufacture.

6.4 Special precautions for storage:

Store at a temperature below 30°C.

6.5 Nature and contents of container:

Heparin Injection is available as a 10 x 5ml clear glass vial containing 25000 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: 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