## 1. Name of the medicinal Product

Heparin Injection BP 5000 IU / ml(HEPALIN)

## 2. Qualitative and Quantitative Composition

**Qualitative declaration**

Each vial with 5 ml solution for injection contains 25,000 I.U. of sodium heparin.

**Excipient with known effect:** Benzyl alcohol (10 mg/ml), sodium (3.086 mg/ml).

**Quantitative declaration**

For full list of Excipients, see section 6.1.

## 3. Pharmaceutical Form

Solution for Injection

Distribution category: POM

A clear colourless solution or straw colour solution, free from turbidity & matter with deposit on standing.

## 4. Clinical Particulars

### *4.1. Therapeutic Indications*

Treatment of thrombo-embolic disorders as deep vein thrombosis, acute arterial embolism or thrombosis, thrombophlebitis, pulmonary embolism, fat embolism. Prophylaxis of deep vein thrombosis and thromboembolic events.

### *4.2. Posology and Method ofAdministration*

**Route of administration:**

By continuous IV infusion in 5% glucose or 0.9% sodium chloride or by intermittent IV or by SC injection. As effects of heparin are short-lived, administration by IV infusion or SC injection is preferable to intermittent IV injections. The intravenous injection volume of heparin injection should not exceed 15ml. Heparin is not effective by oral administration and should be given by intermittent IV injection, intravenous infusion, or deep subcutaneous (intrafat, i.e., above the iliac crest or abdominal fat layer) injection.

**Recommended dosage**

***Prophylaxis of deep vein thrombosis and pulmonary embolism***

Adults: 2 hours pre-operatively: 5,000 units SC, followed by 5,000 units SC every 8-12 hours, for 7-10 days or until patient is fully ambulant. For monitoring, anti-Xa assays should be considered as activated partial thromboplastin time (APTT) is not significantly prolonged.

During pregnancy: 5,000 - 10,000 units every 12 hrs, SC, adjusted as per APTT or anti-Xa assay.

Elderly: Dosage reduction and monitoring of APTT may be advisable.

Children: No dosage recommendations.

***Treatment of deep vein thrombosis and pulmonary embolism***

Adults: Loading dose: 5,000 units IV (10,000 units may be in severe pulmonary embolism).

Maintenance: 1,000-2,000 units/hour by IV infusion, or 10,000-20,000 units 12 hourly SC, or 5,000-10,000 units 4-hourly by IV injection.

Elderly: Dosage reduction may be advisable.

Children and small adults: Loading dose: 50 units/kg IV.

Maintenance: 15-25 units/kg/hour by intravenous infusion, or 250 units/kg 12 hourly SC or 100 units/kg 4-hourly by IV injection.

***Treatment of unstable angina pectoris and acute peripheral arterial occlusion***

Adults: Loading dose: 5,000 units IV.

Maintenance: 1,000-2,000 units/hour by IV infusion, or 5,000-10,000 units 4-hourly by IV injection.

Elderly: Dosage reduction may be advisable.

Children and small adults: Loading dose: 50 units/kg intravenously

Maintenance: 15-25 units/kg/hour by IV infusion, or 100 units/kg 4-hourly by IV injection.

Daily laboratory monitoring is essential during full-dose heparin treatment with APTT.

***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 activated clotting time (ACT) in the 400-500 seconds range.

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: Altered heparin responsiveness or resistance may require dosage adjustment to achieve the desired effect.

### *4.3. Contraindications*

Heparin Injection BP 5000 IU/ml should not be used in case of: Hypersensitivity to heparin or any other constituent of the preparation. Patients with present or previous thrombocytopenia (type II) caused by heparin. Diseases accompanied by increased bleeding tendency e.g. hemorrhagic diathesis, clotting factor deficiencies (except disseminated intravascular coagulation during the phase of hypercoagulation) severe hepatic, renal or pancreatic diseases, severe thrombocytopenia. Diseases with a suspicion of damage to the vascular system, such as: gastric ulcers and/or intestinal ulcers, hypertension (above 105 mmHg diastolic), intra-cerebral hemorrhage, injury or surgery of the central nervous system, eye surgeries, retinopathies, intravitreal hemorrhage, aneurysm of cerebral arteries, sub-acute bacterial endocarditis. Must not be given to premature children up to 3 yrs old or neonates (contains benzyl alcohol). It may cross the placenta the use of this formulation must be avoided in pregnancy.

### *4.4. Special warnings and precautions foruse*

Heparin Injection BP 5000 IU/ml should not be used in case of: Suspicion of a malignant disease with tendency to hemorrhages, Renal and ureteral calculi, Chronic alcoholism.
An especially meticulous medical monitoring is required: During pregnancy, especially in case of long term use, In elderly patients, especially women when concomitantly treated with fibrinolytics or oral anticoagulants, with platelet aggregation inhibitors (for example Acetyl Salicylic Acid, Ticlopidin, Clopidrogrel) and/or Glycoprotein IIb/IIIa receptor antagonists. When concomitantly treated with drugs that increase serum potassium level. The serum potassium level should be monitored in high-risk patients (patients with increased risk of hyperkalemia such as diabetes mellitus, impaired renal function or treatment with serum-potassium level raising medication. With infants, children and patients with kidney and/or liver insufficiency a meticulous supervision and control of coagulation values is required. The same applies also for thrombo-embolism prophylaxis ("low-dose" treatment).
During treatment with Heparin Injection intramuscular injections are to be avoided due to risk of hematomas. Patients treated with Heparin Injection (over 22,500 I.U/day) should avoid all and any risk of being injured.
Heparin induced thrombocytopenia: Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%.

Platelet counts should be obtained at baseline and periodically during heparin administration. 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 (see Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis), the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

Type II Heparin-induced Thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. Type II HIT may progress to the development of venous and arterial thromboses, a condition referred to as Heparin-induced Thrombocytopenia and Thrombosis (HITT).

Thrombotic events may also be the initial presentation for HITT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/µl or if recurrent thrombosis develops, the heparin product should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Type II Heparin-induced Thrombocytopenia (HIT) and Type II HIT and Thrombosis can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for Type II HIT and Type II HIT and thrombosis. Platelet count controls should be carried out. Before starting heparin administration. One day after starting heparin administration. Afterwards during first three weeks at regular intervals every three to four days.

Furthermore a control of platelet count is recommended at the end of heparin administration. Heparin may falsify numerous laboratory results, e.g. erythrocyte sedimentation rate, erythrocyte resistance and complement fixation examination.

Heparin may affect the prothrombin time; this must be considered during adjustment to coumarine derivatives. Tests on thyroid function might be falsified during heparin therapy (e.g. false high levels of T3 and T4).

**Pregnancy and lactation:** As it contain benzyl alcohol may cross the placenta, the use of this formulation should be avoided during pregnancy. Heparin does not cross the placenta or

appear in breast milk. The decision to use heparin in pregnancy should be taken after evaluation of the risk/benefit in any particular circumstances.
Reduced bone density has been reported with prolonged heparin treatment during pregnancy.
Hemorrhage may be a problem during pregnancy or after delivery, During birth, epidural anesthesia is absolutely contra-indicated in pregnant women treated with anticoagulants.
This product contains 25 mg sodium per 5 ml clear glass vial /each ml, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Caution for use; it is contain benzyl alcohol (10 mg/ml) as preservatives. Caution should be used if prescribing Heparin Injection to susceptible patients. Benzyl alcohol may cause toxic reactions and anaphylactic reactions in infants and children up to three years old.

4.5. ***Interaction with other medicinal products and other forms of interaction*** Substances that can influence plasma blood coagulation or the cells involved in this process may cause a tendency toward increased bleeding (such substances are, for example, acetyl salicylic acid, Ticlopidin, Clopidogrel, glycoprotein, IIb/IIIa receptor antagonists, coumarine derivatives, fibrinolytics, dipyridamol, dextranes, high dose penicillin therapy). An enhanced heparin effect in concomitant administration of non-steroidal anti-inflammatory drugs (such as Phenobutazone, Indomethacin, Sulfinpyrazone) is possible.
When alkaline medications such as tricyclic psychotropics, antihistamines and quinine are concomitantly administered, salt formation with heparin can cause loss of efficacy of both drugs.
An intravenous infusion of nitroglycerine might cause a reduction of the effectiveness of Heparin. A removal of nitroglycerine might cause a rapid increase of aPTT. Close controls of PTT together with a dosage adjustment of Heparin are necessary with the simultaneous infusion of nitroglycerine. An increased effect of other drugs e.g. Propranolol, can occur through plasma protein binding displacement.
Medication increasing serum potassium levels can only be used under especially close medical monitoring together with heparin injection BP 5000 IU/ML.
In addition, heparin shows numerous interactions with other preparations, whose clinical significance is being evaluated differently.

***4.6. Pregnancy and Lactation***

**Pregnancy and lactation**: As it contains benzyl alcohol may cross the placenta, the use of this formulation should be avoided during pregnancy. Heparin does not cross the placenta or appear in breast milk. The decision to use heparin in pregnancy should be taken after evaluation of the risk/benefit in any particular circumstances.

Reduced bone density has been reported with prolonged heparin treatment during pregnancy. Haemorrhage may be a problem during pregnancy or after delivery, During birth, epidural anesthesia is absolutely contra-indicated in pregnant women treated with anticoagulants.

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### *4.7. Effects on ability to Drive and use Machines*

None stated

### *4.8. Undesirable effect*

Haemorrhage, Adrenal insufficiency secondary to adrenal haemorrhage.

Occasional thrombocytopenia has been observed. 2 types of heparin-induced thrombocytopenia have been defined. Type I is frequent, mild (usually >50 x 109/L) and transient, occurring within 1-5 days of heparin administration. Type II is less frequent but often associated with severe thrombocytopenia (usually <50 x 10 /L). Heparin should be discontinued immediately.

Prolonged dosing with heparin may cause alopecia and osteoporosis. Significant bone demineralisation has been reported in women taking more than 10,000 I.U. per day of heparin for at least 6 months.

Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalemia may occur particularly in patients with chronic renal failure and diabetes mellitus.

Hypersensitivity reactions to heparin are rare such as urticaria, conjunctivitis, rhinitis, asthma, cyanosis, tachypnoea, feeling of oppression, fever, chills, angioneurotic oedema and anaphylactic shock. Rare local irritation and skin necrosis may occur. 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. Priapism has been reported.

Increased serum transaminase values may occur but usually resolve on discontinuation of heparin. Heparin administration is associated with release of lipoprotein lipase into the plasma; rebound hyperlipidaemia may follow heparin withdrawal.

### *4.9. Overdose*

Haemorrhage is potential hazard of heparin therapy, usually due to overdosage and minimised by strict laboratory control. Nosebleeds, blood in urine, or tarry stools may be noted as the first sign of bleeding. Slight haemorrhage can usually be treated by withdrawing the drug. Prolonged clotting time will indicate presence of an excessive anticoagulant effect requiring neutralisation by intravenous protamine sulphate, at a dosage of 1mg for every 100 I.U. of heparin to be neutralised. The bolus dose of protamine sulphate should be given slowly over about 10 minutes and not exceed 50 mg. If more than 15 minutes have elapsed since injection of heparin, lower doses of protamine will be necessary. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions often resembling anaphylaxis have been reported.

## 5. Pharmacological Properties

### 5.1. *Pharmacodynamics Properties*

Pharmacotherapeutic Group: Antithrombotic
agents ATC Code: B01AB01

Heparin is an anticoagulant and acts by inhibiting thrombin and by potentiating naturally occurring inhibitors of activated Factor X (Xa). Heparin acts at multiple sites in normal coagulation system. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of fibrin-stabilizing factor. Heparin does not have fibrinolytic activity & will not lyse existing clots.

### *5.2. Pharmacokinetic Properties*

As heparin is not absorbed from the gastrointestinal tract and sublingual sites, it is administered by injection. After injection heparin extensively binds to plasma proteins. Heparin is metabolised in the liver, reticulo-endothelial systems and the inactive metabolic products are excreted in the urine. The half-life of heparin is dependent on the dose. Peak plasma levels of heparin are achieved 2 to 4 hours following subcutaneous administration.

### *5.3. Preclinical Safety Data*

No long-term carcinogenicity studies and reproduction studies in animals have been performed to evaluate potential of heparin concerning mutagenesis or impairment of fertility.

## 6. Pharmaceutical Particulars

### 6.1. *ListofExcipients*

Sodium Chloride
Benzyl Alcohol
Hydrochloric Acid
Sodium Hydroxide
Water for Injections

### *6.2. Incompatibilities*

Not applicable

### *6.3. Shelf Life*

24 Months
Use the solution within 28 days after first opening the container

### *6.4. Special Precautions for Storage*

Do not store above 30°C. Protect from light. Do not freeze.

### *6.5. Nature and contents ofcontainer*

A clear colourless or straw colour solution filled in 5 ml Clear Glass Vial. such 1 vial is in the Printed carton with Packing Insert.

### *6.6. Special precautions for disposal and other handling*

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. Marketing Authorization Holder and Manufacturing Site Addresses

### 7.1. Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,

District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

**7.2. Name and Address of Manufacturing Site(s)**

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

**8. Marketing Authorization Number**

TAN 22 HM 0245

**9. Date of First <Registration> / Renewal of The <Registration>**

19th July, 2022

**10. Date of Revision of the Text**