SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Heparin Injection BP 5000 IU/ml Solution for Injection - Hepanir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml Contains

Heparin sodium BP	5000 IU
Benzyl alcohol (as preservative) BP	0.95% w/v
Water for Injections BP	q.s.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of deep vein thrombosis and pulmonary embolism

Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and acuteperipheral arterial occlusion.

Prophylaxis of mural thrombosis following myocardial infarction.

In extracorporeal circulation and hemodialysis.

4.2 Posology and method of administration

Posology

Route of administration

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

As the effects of heparin are short-lived, administration by intravenous infusion or subcutaneousinjection is preferable to intermittent intravenous injections.

Recommended dosage

Prophylaxis of deep vein thrombosis and pulmonary embolism

Adults:

2 hours preoperatively: 5,000 units subcutaneously

Followed by: 5,000 units subcutaneously every 8-12 hours, for 7-10 days or until the patient is fully ambulant.

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

During pregnancy: 5,000 - 10,000 units every 12 hours, subcutaneously, adjusted according to 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 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.

4.3 Contraindications

Heparin should not be administered by intramuscular injection or after major trauma.

Patients who consume large amounts of alcohol, who are sensitive to the drug, who are actively bleeding or who have hemophilia or other bleeding disorders, severe liver disease (including oesophageal varices), purpura, severe hypertension, active tuberculosis or increased capillary permeability.

Patients with present or previous thrombocytopenia. The rare occurrence of skin necrosis in patients receiving heparin contra-indicates the further use of heparin either by subcutaneous or intravenous routes because of the risk of thrombocytopenia.

Because of the special hazard of post-operative hemorrhage heparin is contra-indicated during surgery of the brain, spinal cord and eye, in procedures at sites where there is a risk of bleeding, in patients that have had recent surgery, and in patients undergoing lumbar puncture or regional anesthetic block.

The relative risks and benefits of heparin should be carefully assessed in patients with a bleeding tendency or those patients with an actual or potential bleeding site eg. Hiatus hernia,

peptic ulcer, neoplasm, bacterial endocarditis, retinopathy, bleeding hemorrhoids, suspected intracranial hemorrhage, cerebral thrombosis or threatened abortion.

In patients receiving heparin for treatment rather than prophylaxis, locoregional anesthesia in elective surgical procedures is contraindicated because use of heparin may be very rarely associated with epidural or spinal hematoma resulting in prolonged or permanent paralysis. If such a procedure is planned the heparin should be stopped and the procedure should be delayed until the aPTT has returned to normal. Epidural anesthesia use during birth in pregnant women treated with heparin is contraindicated.
Menstruation is not a contra-indication.
Concomitant use of intravenous diclofenac with heparin (including low dose heparin) is contraindicated.

4.4 Special warnings and precautions for use

Platelet counts should be measured in patients receiving heparin treatment for longer than 5 daysand the treatment should be stopped immediately in those who develop thrombocytopenia.

Heparin induced thrombocytopenia (HIT) and heparin induced thrombocytopenia withthrombosis (HITT) can occur up to several weeks after discontinuation of heparin therapy.
Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin shouldbe evaluated for HIT or HITT.

In patients with advanced renal or hepatic disease, a reduction in dosage may be necessary. Therisk of bleeding is increased with severe renal impairment and in the elderly (particularly elderlywomen).

Although heparin hypersensitivity is rare, it is advisable to give a trial dose of 1,000 I.U. inpatients with a history of allergy. Caution should be exercised in patients with knownhypersensitivity to low molecular weight heparins.

In most patients, the recommended low-dose regimen produces no alteration in clotting time.However, patients show an individual response to heparin, and it is therefore essential

that theeffect of therapy on coagulation time should be monitored in patients undergoing major surgery.

Caution is recommended in patients receiving heparin prophylactically and undergoing spinal orepidural anaesthesia or spinal puncture (risk of spinal or epidural haematoma resulting inprolonged or permanent paralysis). The risk is increased by the use of a peridural or spinalcatheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as nonsteroidalanti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants and bytraumatic or repeated puncture.

In decision making on the interval between the last administration of heparin at prophylacticdoses and the placement or removal of a peridural or spinal catheter, the product characteristicsand 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 anticoagulation in the context of peridural or spinalanaesthesia, 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 a nurse or clinician immediately if they experience any of these.

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly inpatients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolicacidosis, a raised plasma potassium, or taking potassium sparing drugs. The risk of hyperkalemia 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 in all patients treated for more than 7 days**.**

Heparin resistance

There is considerable variation in individual anticoagulant responses to heparin.

Heparin resistance, defined as an inadequate response to heparin at a standard dose for achieving a therapeutic goal occurs in approximately 5 to 30% of patients.

Factors predisposing to the development of heparin resistance, include:

• Antithrombin III activity less than 60% of normal (antithrombin III-dependent heparinresistance):

Reduced antithrombin III activity may be hereditary or more commonly, acquired (secondary to preoperative heparin therapy in the main, chronic liver disease, nephrotic syndrome, cardiopulmonary bypass, low grade disseminated intravascular coagulation or drug induced, e.g. by aprotinin, oestrogen or possibly nitroglycerin)

• Patients with normal or supranormalantithrombin III levels (antithrombin III-independent heparin resistance)

- Thromboembolic disorders
- Increased heparin clearance

• Elevated levels of heparin binding proteins, factor VIII, von Willebrand factor, fibrinogen, platelet factor 4 or histidine-rich glycoprotein

- Active infection (sepsis or endocarditis)
- Preoperative intra-aortic balloon counterpulsation
- Thrombocytopenia
- Thrombocytosis
- Advanced age
- Plasma albumin concentration ≤ 35g/dl
- Relative hypovolaemia

Heparin resistance is also often encountered in acutely ill patients, in patients with malignancy and during pregnancy or the post-partum period.

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

4.5 Interaction with other medicinal products and other forms of interaction

Analgesics: Drugs that interfere with platelet aggregation eg. Aspirin and other NSAIDs should be used with care. Increased risk of haemorrhage with;

- Ketorolac
- Intravenous diclofenac

Avoid concomitant use of either ketorolac or intravenous diclofenac, even with low – dose heparin.

Anticoagulants, platelet inhibitors, etc: Increased risk of bleeding with oral anticoagulants,epoprostenol, clopidogrel, ticlopidine, streptokinase, dipyridamole, dextran solutions, abciximab, eptifibatide or any other drug which may interfere with coagulation.

Cephalosporins: Some cephalosporins, e.g. cefaclor, cefixime and ceftriaxone, can affect the coagulation process and may therefore increase the risk of haemorrhage when used concurrently with heparin.

ACE inhibitors, angiotensin-II receptor antagonists or the renin inhibitor aliskiren:

Hyperkalaemia may occur with concomitant use.

Nitrates: Reduced activity of heparin has been reported with simultaneous intravenous glyceryl trinitrate infusion.

Probenecid: May increase the anticoagulant effects of heparin.

Tobacco smoke: Nicotine may partially counteract the anticoagulant effect of heparin. Increased heparin dosage may be required in smokers.

Interference with diagnostic tests may be associated with pseudo-hypocalcaemia (in haemodialysis patients), artefactual increases in total thyroxine and triiodothyronine, simulated metabolic acidosis and inhibition of the chromogenic lysate assay for endotoxin. Heparin may interfere with the determination of aminoglycosides by immunoassays.

4.6 Fertility, pregnancy and lactation

Heparin is not contraindicated in 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.

Osteoporosis has been reported with prolonged heparin treatment during pregnancy.

Particular caution is required at the time of delivery. Due to the risk of uteroplacental haemorrhage, heparin treatment should be stopped at the onset of labour.

If epidural anaesthesia is envisaged, heparin treatment should be suspended whenever possible.

Use in women with threatened abortion is contraindicated.

4.7 Effects on ability to drive and use machines

None stated

4.8 Undesirable effects

Blood disorders:

Haemorrhage

Thrombocytopenia has been observed occasionally. It has been reported that thrombocytopenia occurs more frequently with bovine-derived heparin than porcine-derived heparin**.** Two types of heparin-induced thrombocytopenia have been defined. Type I is

frequent, mild (usually >50 x109/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 109/L). It is immune-mediated and occurs after a week or more (earlier in patients previously exposed to heparin). It is associated with the production of a platelet-aggregating antibody and thromboembolic complications, due to platelet-rich thrombi (the 'white clot syndrome'), which may precede the onset of thrombocytopenia. Pulmonary embolism has been reported as thromboembolic complications of heparin-induced thrombocytopenia. Heparin should be discontinued immediately in patients who develop thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia andthrombosis (HITT) 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 HIT and HITT.

Endocrine disorders:

Adrenal insufficiency secondary to adrenal haemorrhage has been associated with heparin(rarely). 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.

Hepatic disorders:

Increased serum transaminase values may occur but usually resolve on discontinuation ofheparin.

Immune system disorders:

Hypersensitivity reactions to heparin are rare. They include urticaria, conjunctivitis, rhinitis,asthma, cyanosis, tachypnoea, and feeling of oppression, fever, chills, angioneuroticoedema andanaphylactic shock.

Metabolic disorders:

Heparin administration is associated with release of lipoprotein lipase into the plasma; rebound hyperlipidaemia may follow heparin withdrawal.

Muscle and tissue disorders:

There is some evidence that prolonged dosing with heparin (i.e. over many months) may cause osteoporosis and fractures in the vertebra and ribs**.** Significant bone demineralisation has been reported in women taking more than 10,000 I.U. per day of heparin for three months or longer.

Reproductive and breast disorders:

Priapism has been reported.

Skin and subcutaneous tissue disorders:

Local irritation and skin necrosis may occur but are rare. There is some evidence that prolonged dosing with heparin (i.e. over many months) may cause alopecia.

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.

Pruritus Rash (including erythematous and maculopapular)

Vascular disorders:

Haematoma. Very rare cases of epidural and spinal haematoma have been reported in patientsreceiving heparin for prophylaxis undergoing spinal or epidural anaesthesia or spinal puncture.

4.9 Overdose

A potential hazard of heparin therapy is hemorrhage, but this is usually due to over dosage and the risk is minimized by strict laboratory control. Slight hemorrhage can usually be treated by withdrawing the drug. If bleeding is more severe, clotting time and platelet count should be determined. Prolonged clotting time will indicate the presence of an excessive anticoagulant effect requiring neutralization by intravenous protamine sulfate, at a dosage of 1 mg for every 100 I.U. of heparin to be neutralized. The bolus dose of protamine sulfate should be given slowly over about 10 minutes and not exceed 50 mg. If more than 15 minutes have elapsed since the injection of heparin, lower doses of protamine will be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Heparin is an anticoagulant and acts by inhibiting thrombin and by potentiating the naturally occurring inhibitors of activated Factor X (Xa).{group},

ATC code: B01AB01

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 metabolized in the liver and the inactive metabolic products are excreted in the urine. The half-life of heparin is dependent on the dose.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride BP

Benzyl alcohol BP

Water for Injections BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months from the date of manufacture

6.4 Special precautions for storage

Store in dry & dark place, at a temperature not exceeding 30oC.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Heparin Injection is packed in 5 ml amber glass vial USP type I closed with grey Bromobutylrubber stopper sealed with flip off seal. Each 5 ml vial is packed in baby carton with packageinsert. Such 10 baby cartons are packed in one mother carton.

6.6 Special precautions for disposal <and other handling>

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

08786/3586/NMR/2017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29.06.2023

Date of latest renewal: Not Applicable

10. DATE OF REVISION OF THE TEXT

12.07.2023