SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Heparin sodium 1,000 IU/mL solution for injection or concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin sodium 1,000 IU/mL solution for injection or concentrate for solution for infusion

Each mL contains 1,000 units of heparin sodium (from porcine intestinal mucosa).

Each vial contains 5 mL. One vial contains 5,000 units of heparin sodium.

Excipient(s) with known effect: Sodium methylparaben (E-219), Sodium propylparaben (E217) and sodium.

Each 1,000 units/mL vial contains 20.73 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for infusion

Clear solution, practically free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

In extracorporeal circulation and haemodialysis.

4.2 Posology and method of administration

Posology

Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris, acute peripheral arterial occlusion

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 5,000-10,000 units 4-hourly by intravenous injection.

Elderly:
Dosage reduction may be advisable.

Children and adolescents:

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.

In extracorporeal circulation and haemodialysis

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:

Loading dose: 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 (see section 4.4).

Method of administration

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

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

Heparin should not be administered by intramuscular injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

After major trauma, 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 anaesthetic block.

Patients who consume large amounts of alcohol, who have generalised or local haemorrhagic tendency, who are actively bleeding, have haemophilia or other bleeding disorders, including 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 contraindicates the further use of heparin either by subcutaneous or intravenous routes because of the risk of thrombocytopenia.

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 haemorrhoids, suspected intracranial haemorrhage, cerebral thrombosis or threatened abortion.

In patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedures is contraindicated because use of heparin may be very rarely associated with epidural or spinal haematoma 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 anaesthesia use during birth in pregnant women treated with heparin is contraindicated (see section 4.6).

Threatened abortion.

Menstruation is not a contra-indication.

Concomitant use of intravenous diclofenac (including low dose heparin) is contraindicated.

4.4 Special warnings and precautions for use

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 e.g. hiatus hernia, peptic ulcer, neoplasm, bacterial endocarditis, retinopathy, bleeding haemorrhoids, suspected intracranial haemorrhage, cerebral thrombosis or. Care should also be taken when heparin is administered to patients with hypertension, renal or hepatic insufficiency.

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 (HIT) and heparin induced thrombocytopenia with thrombosis (HITT) 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 HIT or HIT. In patients with advanced renal or hepatic disease, a reduction in dosage may be necessary. The risk of bleeding is increased with severe renal impairment and in the elderly (particularly elderly women).

Although heparin hypersensitivity is rare, it is advisable to give a trial dose of 1,000 I.U. in patients with a history of allergy. Heparin should be used with caution in patients with hypersensitivity 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 the effect of therapy on coagulation time should be monitored in patients undergoing major surgery.

Caution is recommended in patients receiving heparin prophylactically and undergoing spinal or epidural anaesthesia or spinal puncture (risk of spinal or epidural haematoma resulting in prolonged or permanent paralysis). The risk is increased by the use of a peridural or spinal catheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), 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 peridural 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.

In patients receiving heparin for treatment rather than prophylaxis, locoregional 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. If such a procedure is planned the heparin should be stopped and the procedure should be delayed until the aPTT has returned to normal.

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 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, a 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 in all patients treated for more than 7 days.

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

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 heparin resistance):

  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 supranormal antithrombin 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 $\leq$ 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 (see section 4.5).

Excipients

Heparin contains methyl- and propyl parahydroxybenzoate and sodium as excipients. Methyl- and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Heparin sodium 1,000 IU/mL solution for injection or concentrate for solution for infusion

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

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 (see section 4.3)

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

Pregnancy

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.

Epidural anaesthesia use during birth in pregnant women treated with heparin is contraindicated. If epidural anaesthesia is envisaged, heparin treatment should be suspended whenever possible.

Use in women with threatened abortion is contraindicated (refer to section 4.3).

Breast-feeding
Heparin does not cross the placenta or appear in breast milk.

4.7 Effects on ability to drive and use machines

Heparin has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Blood and lymphatic system disorders

Haemorrhage (see section 4.4 and 4.9).

Thrombocytopenia has been observed occasionally (see section 4.4). 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 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 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 and thrombosis (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.

Immune system disorders

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

Metabolism and nutrition disorders

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

Vascular disorders

Haematoma. Very rare cases of epidural and spinal haematoma have been reported in patients receiving heparin for prophylaxis undergoing spinal or epidural anaesthesia or spinal puncture (see Section 4.4).

Hepatobiliary disorders

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

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 (see section 4.4).

Skin and subcutaneous tissue disorder

Local irritation and skin necrosis may occur but are rare. If this occurs treatment must be withdrawn immediately.

Alopecia: there is some evidence that prolonged dosing with heparin (i.e. over many months) may cause alopecia.

Pruritus

Rash (including erythematous and maculopapular)

Musculoskeletal and connective 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 system and breast disorders

Priapism has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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4.9 Overdose

A potential hazard of heparin therapy is haemorrhage, but this is usually due to overdosage and the risk is minimised by strict laboratory control. Slight haemorrhage 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 neutralisation by intravenous protamine sulfate, at a dosage of 1 mg for every 100 I.U. of heparin to be neutralised. 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: Antithrombotic agents, ATC code: B01AB01

Heparin is an anticoagulant and acts by inhibiting thrombin and by potentiating the naturally occurring inhibitors of activated Factor X (Xa).

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 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 preclinical data of relevance to the prescriber which are additional to that already included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium methylparahydroxybenzoate (E219)

Sodium propylparahydroxybenzoate (E217)

Sodium Chloride

Hydrochloric acid (for pH adjustment)

Sodium Hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Heparin is incompatible with many injectable preparations e.g. some antibiotics, opioid analgesics and antihistamines.

The following drugs are incompatible with heparin:

Alteplase, amikacin sulfate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin potassium or sodium, cefalotin sodium, chlorpromazine hydrochloride, ciprofloxacin lactate, cisatracurium besilate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulfate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulfate, labetolol hydrochloride, levofloxacin, meticillin sodium, methotrimeprazine, netilmicin sulfate, nicardipine hydrochloride, oxytetracycline hydrochloride, pethidine hydrochloride, polymyxin B sulfate, promethazine hydrochloride, streptomycin sulfate, tobramycin sulfate, trifluprom azine hydrochloride, vancomycin hydrochloride, vinblastine sulfate and vinorelbine tartrate.

Dobutamine hydrochloride and heparin should not be mixed or infused through the same intravenous line, as this causes precipitation.

Heparin and reteplase are incompatible when combined in solution. If reteplase and heparin are to be given through the same line this, together with any Y-lines, must be thoroughly flushed with a 0.9% saline or a 5% glucose solution prior to and following

the reteplase injection.

6.3 Shelf life

4 years

This medicinal product does not require any special storage conditions.

Do not freeze.

Chemical and physical in use stability has been demonstrated for 28 days at 25ºC.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 25ºC.

Other in-use storage times and conditions are the responsibility of the user.

Shelf-life after dilution

Chemical and physical in-use stability of admixtures of Heparin 1000 IU/mL & 5000 IU/mL at concentration of 47.6 IU/mL and 455 IU/mL are stable at 25ºC± 2ºC within 72h with 5% Glucose or 0.9% NaCl diluents.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Chemical and physical in use stability has been demonstrated for 28 days at 25ºC.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 25ºC.

Other in-use storage times and conditions are the responsibility of the user.

For storage conditions after first opening and after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Available in packs of 1, 5 and 10 vials containing 5 ml multidose solution for injection.

Not all the packs sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Each multidose vial should be restricted to use in a single patient.

7 MARKETING AUTHORISATION HOLDER

Reig Jofre UK Ltd,

Follaton House, Plymouth Road, Totnes, Devon, TQ9 5NE, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 44095/0040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/04/2025

10 DATE OF REVISION OF THE TEXT

03/04/2025