Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Heparin sodium 5,000 I.U./ml Solution for injection or concentrate for solution for infusion, 5 ml vials

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin sodium 5,000 I.U./ml (25,000 I.U. in 5 ml)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for infusion.
A colourless or straw-coloured liquid, free from turbidity and from matter that deposits on standing.

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 acute peripheral arterial occlusion.

Prophylaxis of mural thrombosis following myocardial infarction.

In extracorporeal circulation and haemodialysis.

4.2 Posology and method of administration

Route 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.

Recommended dosage

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 is 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.

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 1-5,000 units,
Maintenance: 1-2,000 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.

4.3 Contraindications

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

Must not be given to premature babies or neonates (contains benzyl alcohol).

Patients who consume large amounts of alcohol, who are sensitive to the drug, who are actively bleeding or who have haemophilia 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 haemorrhage 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 anaesthetic 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 haemorrhoids, suspected intracranial haemorrhage, cerebral thrombosis or threatened abortion.

Menstruation is not a contra-indication.

4.4 Special warnings and precautions for use

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

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. Caution should be exercised in patients with known hypersensitivity to low molecular weight heparins. Heparin Injection contains benzyl alcohol (10mg/ml) and methyl parahydroxybenzoate 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. Methyl Parahydroxybenzoate may cause allergic reactions (possibly delayed) and exceptionally bronchospasm.

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 spinal or epidural anaesthesia (risk of spinal haematoma).

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, 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 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 predisposine to the development of heparin resistance, include:

o 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)

o Patient with normal or supranormal antithrombin III levels (antithrombin III-independent heparin resistance).
o Thromboembolic disorders

o Increased heparin clearance

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

o Active infection (sepsis or endocarditis)

o Preoperative intra-aortic balloon counterpulsation

o Thrombocytopenia

o Thrombocytosis

o Advanced age

o Plasma albumin concentration ≤ 35g/dl

o Relative hypovolaemia

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

4.5 Interaction with other medicinal products and other forms of interactions

Analgesic: Drugs that interfere with platelet aggregation e.g. aspirin, and other NSAIDs, should be used with care. Increased risk of haemorrhage with ketoralac (avoid concomitant use even with low-dose heparin).

Anticoagulants, platelet inhibitors, etc: Increased risk of bleeding with oral anticoagulants, epoprostenol, clopidogrel, ticlopidine, streptokinase, dipyridamole, dextran solutions, 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: 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 test may be associated with pseudo-hypocalcaemia (in haemodialysis patients), artefactual increases in total thyroxine and triiodothyronnie, 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.
Reduced bone density has been reported with prolonged heparin treatment during pregnancy.
Haemorrhage may be a problem during pregnancy or after delivery.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Haemorrhage (see also Special Warnings and Precautions and Overdosage Information).

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

Thrombocytopenia has been observed occasionally (see also Special Precautions and Warning). Two types of heparin-induced thrombocytopenia have been difined. Type I is frequent, mild (usually >50 x 10^9/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 10^9/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 which may precede the onset of thrombocytopenia. Heparin should be discontinued immediately.

There is some evidence that prolonged dosing with heparin (ie. over many months) may cause alopecia and osteoporosis. Significant bone demineralisation has been reported in women taking more than 10,000 iu 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 *(see Warnings and Precautions)*.

Hypersensitivity reactions to heparin are rare. They include urticaria, conjunctivitis, rhinitis, asthma, cyanosis, tachypnoea, feeling of oppression, fever, chills, angioneurotic oedema and anaphylactic shock. In some instances the precipitating agent will prove to be the preservative rather than the heparin itself.

Local irritation and skin necrosis may occur but are rare. 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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Methyl parahydroxybenzoate (E218)
Water for injections
Sodium hydroxide
Hydrochloric acid

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, 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 and vinblastine sulfate.

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

3 years

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

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 25°C. Other in use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

5 ml multidose neutral glass (Type 1, Ph. Eur.) vial. Carton contains 10 vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/229/005

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10 DATE OF REVISION OF THE TEXT

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