Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Heparin sodium 25,000 I.U./ml solution for injection, 0.2ml prefilled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin sodium 25,000 I.U./ml (5,000 I.U. in 0.2 ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.

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

4.2 Posology and method of administration

Route of administration
By subcutaneous injection.

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.

4.3 Contraindications

Patients who consume large amounts of alcohol, who are sensitive to heparin, 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 systemic 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 site 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, ulcerative lesions of the gastrointestinal tract, 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

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.

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.

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.

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 (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 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.

Hyperkalaemia may occur with concomitant ACE inhibitors.
Reduced activity of heparin has been reported with simultaneous intravenous glyceryl trinitrate infusion.

Interference with diagnostic test 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 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 ecaluation 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 I (rarely).

Thrombocytopenia has been observed occasionally *(see also Special Precautions and Warnings).* 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 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 I.U. per day of heparin for at least six 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 urtcaria, conjunctivitism rhinitism asthma, cyanosis, tachypnoea, feeling of oppression, fever, chills, angioneurotic oedema and anaphylactic shock.

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, occuring 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

A potential hazard of heparin therapy is haemorrhage, but 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 overly anticoagulated effect requiring neutralisation by intravenous protamine sulphate, at a dosage of 1 mg 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 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 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 those already included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium hydroxide
Hydrochloride acid

6.2 Incompatibilities

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

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

From a microbiological point of view, unless the method of opening/ reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, 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

0.5ml Becton Dickenson Hypak disposable pre-filled syringe containing 0.2 ml of solution. Cartons contain 50 syringes.

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

Not applicable.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd,
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8 MARKETING AUTHORISATION NUMBER

PA 0409/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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