

PACKAGE LEAFLET: INFORMATION FOR THE USER

HEPARIN SODIUM 5,000 I.U./ml solution for injection or concentrate for solution for infusion
HEPARIN SODIUM 25,000 I.U./ml solution for injection or concentrate for solution for infusion
Contains Preservative

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

The name of your medicine is either heparin sodium 5,000 I.U./ml or heparin sodium 25,000 I.U./ml solution for injection or concentrate for solution for infusion. In the rest of this leaflet it is called heparin injection.

In this leaflet:

1. What heparin injection is and what it is used for
2. Before you are given heparin injection
3. How heparin injection is given
4. Possible side effects
5. How to store heparin injection
6. Further information

1. WHAT HEPARIN INJECTION IS AND WHAT IT IS USED FOR

Heparin belongs to a group of drugs that are called anticoagulants. These help to stop blood clotting. Heparin injection 5,000 I.U./ml or 25,000 I.U./ml is used in conditions where blood vessels may become blocked by blood clots. It is therefore used to treat and prevent:

- blood clots in leg veins (deep vein thrombosis)
- blood clots in the lung (pulmonary embolism) as well as for:
- the treatment of chest pains resulting from disease of the heart arteries (unstable angina pectoris)
- the treatment of severe blockages affecting arteries in the legs (acute peripheral arterial occlusion)
- the prevention of blood clots in the heart following a heart attack (mural thrombosis).

It is also used during heart and lung operations and during kidney dialysis.

2. BEFORE YOU ARE GIVEN HEPARIN INJECTION

Heparin injection should not be given if you:

- are allergic to heparin or any of the other ingredients in your medicine, (see 'What heparin injection contains' section 6 and 'Important information about some of the ingredients of heparin injection' below)
- drink large amounts of alcohol
- are currently bleeding from anywhere in the body, (apart from your normal period which does not stop you being given heparin injection)
- have haemophilia (a genetic disorder which may cause you to bleed excessively) or any other bleeding problem
- have or have ever had thrombocytopenia (a serious blood disorder which prevents blood from clotting properly)
- bruise easily (fragile capillaries) or have lots of purple spots that look like bruises (purpura)
- have very high blood pressure
- are suffering from tuberculosis (TB)
- have had severe skin problems resulting from previous heparin treatment
- are about to have surgery of the brain, spine or eye, a lumbar puncture or local anaesthetic nerve block, or some other procedure where bleeding could be a problem
- have recently had an operation
- suffer from severe liver problems which can lead to bleeding into the oesophagus (gullet)
- have bleeding into the brain.

Heparin injection must not be given to premature or newborn babies.

Speak to your doctor before heparin injection is given if you:

- are over 60 years of age
- have any condition which makes you likely to bleed more easily (for example a stomach ulcer, hiatus hernia, inflammation of the heart, problems in the back of your eye, haemorrhoids (piles), a stroke, cancer or threatened miscarriage), If you are unsure, ask your doctor or nurse.
- suffer from diabetes
- suffer from excess acid or high levels of potassium in your blood or are taking a medicine that may increase the potassium level in your blood (e.g. amiloride, triamterene, eplerenone or spironolactone). If any of these apply you may need to have a blood test before the start of your heparin treatment. If you are unsure, ask your doctor or nurse
- have kidney or liver disease. Your doctor may decide that a lower dose is necessary
- suffer from allergies or have previously had an allergic reaction to low molecular weight (LMW) heparin. A small test dose of heparin sodium injection may be given first.

Your doctor will check your blood if you receive treatment for longer than five days and may do other blood tests if you have major surgery.

Your doctor will take particular care if:

- the patient is an infant or child under three years old
- you have an epidural or an anaesthetic given into the spine.

Taking other medicines

It is very important that you inform your doctor if you are taking, or have recently taken, any other medicines, including those medicines obtained without a prescription, as some medicines may affect the way heparin injection works. Taking some medicines at the same time as heparin may mean you may be likely to bleed more.

In particular, tell your doctor if you are taking any of the following:

- aspirin or other non-steroidal anti-inflammatory drugs (e.g. diclofenac or ibuprofen)
- dextran solutions (used to treat shock)
- medicines which may interfere with the proper clotting of the blood (e.g. dipyridamole, epoprostenol, clopidogrel or streptokinase)
- cephalosporins, used to treat infections
- medicines called ACE inhibitors used for high blood pressure and heart failure (e.g. captopril, enalapril, lisinopril or ramapril)
- medicines that may increase the potassium level in your blood (e.g. amiloride, triamterene, eplerenone or spironolactone)
- glyceryl trinitrate given into a vein (for coronary heart disease)
- aminoglycoside antibiotics (e.g. gentamicin, amikacin, neomycin or tobramycin)
- probenecid, used in the treatment of gout

If you need one of the above medicines your doctor may decide to alter the dose of heparin injection or the other medication. If you have any doubts about whether this medicine should be administered then discuss things more fully with your doctor or nurse before it is given.

Tobacco smoke can also interfere with the working of heparin injection. You should inform your doctor if you smoke.

The presence of heparin in the blood can affect the results of some blood tests such as thyroid tests and the levels of calcium or some antibiotics (e.g. gentamicin) in the blood.

Important information about the ingredients benzyl alcohol and methyl parahydroxybenzoate

The benzyl alcohol in heparin injection may cause toxic reactions and allergic reactions in infants and children up to three years old.

The methyl parahydroxybenzoate in heparin injection may cause allergic reactions (possibly delayed) and exceptionally bronchospasm

Pregnancy and breast-feeding

You should let your doctor or nurse know before you are given heparin injection if you are pregnant or wish to become pregnant.

If you are being given heparin injection bleeding may be a problem during pregnancy or after delivery. Your bones may get thinner if you receive heparin for a long time during pregnancy.

Ask your doctor or nurse for advice if you wish to breast-feed

Driving and using machines

Heparin injection has not been reported to affect ability to drive or operate machines.

3. HOW HEPARIN INJECTION SHOULD BE GIVEN

Your doctor or nurse will inject your dose of heparin into a vein either all at once or over a longer period of time (usually via a drip). Alternatively they may inject your heparin underneath your skin.

The amount injected all at once into a vein should not be greater than 15ml.

You may need to have blood tests if you are receiving higher doses of heparin or if you are pregnant to check on the effects of your heparin treatment.

Heparin injection must not be given to premature or newborn babies.

You may require a lower dose if you have kidney or liver disease.

To PREVENT blood clots in leg veins (deep vein thrombosis) and blood clots in the lung (pulmonary embolism)

Adults

The usual dose of heparin injection in adults is 5,000 units injected under the skin 2 hours before your operation, followed by 5,000 units injected under the skin every 8-12 hours, for 7-10 days or until you are fully able to move about.

Pregnancy

During pregnancy the dosage is 5,000-10,000 units injected under the skin every 12 hours. The dose may be adjusted according to your blood tests.

Elderly

Lower doses may be used in the elderly. You may need to have blood tests if you are elderly, to check on the effects of your heparin treatment.

Children

No specific doses are recommended.

To TREAT blood clots in leg veins (deep vein thrombosis) and blood clots in the lung (pulmonary embolism).

Adults

The usual dose in adults is 5,000 units injected into a vein. This is followed by:

- 1,000-2,000 units/hour injected slowly into a vein or
- 10,000-20,000 units 12 hourly injected under the skin or
- 5,000-10,000 units 4 hourly injected all at once into a vein

Elderly

Lower doses may be used in the elderly



1. NAME OF THE MEDICINAL PRODUCT

Heparin sodium 5,000 I.U./ml solution for injection or concentrate for solution for infusion
Heparin sodium 25,000 I.U./ml solution for injection or concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin sodium 5,000 I.U./ml - Heparin sodium 5,000 I.U./ml (25,000 I.U. in 5ml)
Heparin sodium 25,000 I.U./ml - Heparin sodium 25,000 I.U./ml (125,000 I.U. in 5ml)
For a 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:

Maintenance: Initially 1,000-5,000 units, 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. Also refer to section 4.4, Special warnings and precautions for use.

4.3 Contraindications

Known hypersensitivity to heparin or any of the other ingredients.

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

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.

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 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

Small adults and children

Small adults and children will be given 50 units/kg body weight injected into a vein followed by:

- 15-25 units/kg body weight/hour injected slowly into a vein or
- 250 units/kg body weight 12 hourly injected under the skin or
- 100 units/kg body weight 4 hourly injected all at once into a vein

To TREAT chest pains (unstable angina pectoris) and severe blood clots in the arteries (acute peripheral arterial occlusion) Adults

The usual dose in adults is 5,000 units injected into a vein. This is followed by:

- 1,000-2,000 units/hour injected slowly into a vein or
- 5,000-10,000 units 4 hourly injected all at once into a vein

Elderly

Lower doses may be used in the elderly

Small adults and children

Small adults and children will be given 50 units/kg body weight injected into a vein followed by:

- 15-25 units/kg body weight/hour injected slowly into a vein or
- 100 units/kg body weight 4 hourly injected all at once into a vein

You will have blood tests every day to check the effects of your heparin

To prevent a blood clot in the heart following a heart attack. Adults

The usual dose for adults is 12,500 units 12 hourly injected under the skin for at least 10 days.

Elderly

A lower dose may be needed.

During Heart and Lung Surgery (Adults)

Initially you will be given 300 units/kg body weight. This will be changed according to the results of your blood tests.

During kidney dialysis (Adults)

Initially you will be given 1,000-5,000 units. This will be changed according to the results of your blood tests.

If you think you have been given too much heparin injection

Your doctor will decide which dose is best for you. Too much heparin can cause bleeding. Slight bleeding can be stopped by stopping your heparin treatment. However if you have more severe bleeding you may need blood tests and an injection of a medicine called protamine sulphate. If you think too much medicine has been given to you contact your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, heparin injection may cause side effects in some patients, although not everybody gets them. These are most likely to occur when treatment is first started. You should inform your doctor or nurse immediately if you feel unwell.

Important side effects to look out for:

• **Severe allergic reactions**

Heparin can cause a severe allergic reaction with wheezing, difficulty breathing, a blue tinge to the lips, fever, chills, swelling of the eyes and lips and shock.

Allergic reactions may be due to the ingredients in your heparin rather than the heparin itself. This occurs particularly in infants or children up to three years old.

If you think you are having a severe allergic reaction (see symptoms above) you must tell your doctor or nurse immediately.

• **Bleeding and Bruising**

Heparin injection can reduce the number of cells that help your blood clot (thrombocytopenia) and so can cause bleeding and bruising. This is most likely to occur within the first few days of treatment but may occur later too. The risk of bleeding is increased in the elderly (particularly elderly women).

Signs that you are bleeding more easily include:

- unusual bruising or purple spots on your skin
- unusual bleeding from your gums
- unusual nose bleeds
- blood in your urine (which may cause this to go dark)
- black, tarry-looking stools
- bleeding that will not stop from any operation site or other injury

If you are concerned about unusual bleeding you must tell your doctor or nurse immediately as you may need to stop your heparin.

Other side effects include:

Common side effects (affects 1 to 10 users in 100):

- red lumps or red, itchy patches like eczema often develop 3-21 days after the start of heparin treatment, where injections have been given under the skin

Rare side effects (affects 1 to 10 users in 10,000):

- raised levels of potassium in the blood, particularly in patients with kidney failure or diabetes. If affected you may feel tired and weak.
- allergic reactions including an itchy skin rash, eye irritation, runny nose, wheezing, rapid breathing, a blue tinge to the lips, fever, chills, swelling of the eyes and lips, and shock.
- irritation or sloughing of skin which may occur around the injection site.

Side effects with unknown frequency:

- loss of hair (alopecia) if heparin sodium injection is given over many months
- weakening of the bones (osteoporosis) if heparin sodium injection is given over many months

- persistent erection of the penis (priapism)
- abnormal liver tests
- the amount of a hormone called aldosterone may be lower than normal Your doctor can explain this more.
- high lipid levels on stopping heparin

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting systems listed below.

United Kingdom

Yellow Card Scheme
www.mhra.gov.uk/yellowcard

Ireland

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

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE HEPARIN INJECTION

Keep this medicine out of the reach and sight of children.

Your doctor or nurse will usually be responsible for storing and preparing heparin injection before use and for checking that the vials have not passed their expiry date stated on the carton and the label. The medicine must not be used after the expiry date which is stated on the carton and the label. The expiry date refers to the last day of the month.

Heparin injection should not be given if it shows signs of deterioration such as discolouration.

Do not store above 25°C. Store in the original packaging in order to protect the product from light.

After opening, heparin vials may be kept for 28 days at 25°C, after which they should be discarded.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What heparin injection contains

The active substance is heparin sodium.

1ml of solution of heparin sodium injection 5,000 I.U./ml contains 5,000 international units of the active ingredient. It is available in 5ml multidose vials containing 25,000 I.U. in 5ml of solution.

1ml of solution of heparin sodium injection 25,000 I.U./ml contains 25,000 international units of the active ingredient. It is available in 5ml multidose vials containing 125,000 I.U. in 5ml of solution.

Other ingredients include benzyl alcohol (10mg/ml), methyl parahydroxybenzoate (E218), water for injections, hydrochloric acid and sodium hydroxide.

What heparin injection looks like and contents of the pack

Heparin injection is a colourless or straw-coloured liquid. Each carton contains 10 glass vials.

Other formats

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

| Product Name | Reference Number |
|---|------------------|
| Heparin sodium 5,000 I.U./ml solution for injection or concentrate for solution for infusion | 29831/0110 |
| Heparin sodium 25,000 I.U./ml solution for injection or concentrate for solution for infusion | 29831/0108 |

This is a service provided by the Royal National Institute of Blind People.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

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WOCKHARDT



- Advanced age
- Plasma albumin concentration $\leq 35\text{g/dl}$
- Relative hypovolaemia

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

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 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 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 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 Warnings). Two types of heparin-induced thrombocytopenia have been defined. Type I is frequent, mild (usually $>50 \times 10^9/\text{L}$) and transient, occurring within 1-5 days of heparin administration. Type II is less frequent but often associated with severe thrombocytopenia (usually $<50 \times 10^9/\text{L}$). 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 6 months.

Heparin products can cause hypoadosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalaemia 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 the national reporting system:

United Kingdom

Yellow Card Scheme
www.mhra.gov.uk/yellowcard

Ireland

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 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 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 those already included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Methyl parahydroxybenzoate (E218)
Water for injections
Sodium hydroxide solution
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 sulphate, 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 sulphate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulphate, labetolol hydrochloride, meticillin sodium, methotimeprazine, netilmicin sulphate, nicardipine hydrochloride, oxytetracycline hydrochloride, pethidine hydrochloride, polymyxin B sulphate, promethazine hydrochloride, streptomycin sulphate, tobramycin sulphate, trifluromazine hydrochloride, vancomycin hydrochloride and vinblastine sulphate.

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

36 months

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

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

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

8. MARKETING AUTHORISATION NUMBER(S)

Heparin sodium injection 5,000 I.U./ml –
PL 29831/0110, PA 1339/9/7
Heparin sodium injection 25,000 I.U./ml –
PL 29831/0108, PA 1339/9/8

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

| | |
|---|------------------------------|
| Heparin sodium injection 5,000 I.U./ml | - 20 September 2007 (UK) |
| | - 16 November 2007 (Ireland) |
| Heparin sodium injection 25,000 I.U./ml | - 15 October 2007 (UK) |
| | - 16 November 2007 (Ireland) |

10. DATE OF REVISION OF THE TEXT

December 2015

106923/2

WOCKHARDT