

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

During Heart and Lung Surgery (Adults)

Initially you will be given 300 units/kg. 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:

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

Other ingredients include benzyl alcohol (10mg/ml), methyl parahydroxybenzoate (E218) (as preservatives), 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 1,000 I.U./ml solution for injection or concentrate for solution for infusion	29831/0109

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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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 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 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.

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, labetalol hydrochloride, meticillin sodium, methotrimeprazine, 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)

PL 29831/0109
PA 1339/9/6

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation:
15 October 2007 (UK)
16 November 2007 (Ireland)

10. DATE OF REVISION OF THE TEXT

September 2015

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