DBL™ Heparin Sodium Injection BP

1 NAME OF THE MEDICINE

Heparin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Heparin Sodium Injection BP 1,000 IU/1 mL: each mL contains 1,000 IU Heparin sodium
DBL Heparin Sodium Injection BP 5,000 IU/1 mL: each mL contains 5,000 IU Heparin sodium

DBL Heparin Sodium Injection BP is prepared from porcine intestinal mucosa and is free from pyrogenic substances.

3 PHARMACEUTICAL FORM

DBL Heparin Sodium Injection BP is a colourless or straw-coloured sterile solution of heparin sodium in water for injections. The pH of the injection ranges between 5.0 and 8.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Heparin is indicated for the prophylaxis and treatment of thromboembolic disorders such as thrombophlebitis, pulmonary embolism and occlusive vascular disease. It is also used to prevent thromboembolic complications arising from cardiac and vascular surgery, frostbite, dialysis and other perfusion procedures. Heparin is also used as an anticoagulant in blood transfusions.

4.2 Dose and method of administration

Dosage

Low dose prophylaxis against postoperative venous thromboembolism: heparin sodium may be used. The usual dose is 5,000 units by deep subcutaneous injection 2 hours before surgery and repeated every 8 to 12 hours for 7 days or longer until the patient is fully ambulatory.

Adults

Treatment of established venous thrombosis or pulmonary embolism. Use heparin sodium. Treatment may be given by the following routes:

a) Continuous intravenous infusion: a bolus dose of 5,000 units may be given initially followed by an infusion of 20,000 to 40,000 units in 1 litre of sodium chloride intravenous infusion or glucose intravenous infusion over 24 hours.

b) Intermittent intravenous injection: an initial dose of 10,000 units followed by 5,000 to 10,000 units every 4 to 6 hours may be given.

c) Deep subcutaneous injection: the usual dose is 5,000 units injected intravenously followed by subcutaneous injection of 10,000 units 8 hourly or 15,000 units 12 hourly. A concentrated form of heparin injection should be used (e.g. 25,000 units/mL).

Children

A suggested dosage is 50 units/kg bodyweight initially by intravenous infusion followed by 100 units/kg bodyweight every 4 hours according to the clotting time.

Method of administration

Heparin may be given by intermittent intravenous injection, intravenous infusion or deep subcutaneous injection. It should not be given intramuscularly because of the danger of haematoma formation.

For single patient use. Use once only and discard any residue.

4.3 Contraindications

Heparin therapy is contraindicated in patients who are hypersensitive to the drug.

It should not be used in the following cases:

- in the presence of actual or potential haemorrhagic states, e.g. haemophilia, ascorbic acid deficiency, increased capillary fragility, hiatus hernia, neoplasms, retinopathy, bleeding haemorrhoids or other organic lesions likely to bleed;
- haemorrhagic vascular accident;
- threatened abortion;
- immediate postpartum period;
- subacute bacterial endocarditis or acute infectious endocarditis;
- severe hypertension;
- gastric or duodenal ulcers or other ulcerative conditions which may have a tendency to haemorrhage, e.g. ulcerative colitis;
- advanced renal or hepatic disease;
- during and immediately after spinal or major surgery, especially those involving the brain, eye or spinal cord;
- shock;
- severe thrombocytopenia or a history of thrombocytopenia with any kind of heparin or with pentosan polysulfate;
- patients in whom suitable blood coagulation tests, e.g. whole blood clotting time, partial thromboplastin time, etc., cannot be performed at appropriate intervals (this contraindication refers to full dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low dose heparin).
- hypersensitivity to heparin or to any of the excipients or pork products (e.g. anaphylactoid reactions).

4.4 Special warnings and precautions for use

Heparin should not be given by intramuscular injection, due to the risk of haematoma formation.

When neuraxial anaesthesia (epidural/spinal anaesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with unfractionated heparin or low molecular weight heparins/heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

As heparin is derived from animal tissue, it should be used with caution in patients with a history of allergy or asthma. Before a therapeutic dose is given to such a patient, a trial dose of 1,000 units may be advisable.

Heparin should be used with extreme caution in patients with continuous tube drainage of the stomach or small intestine.

Any action which may cause vascular injury, with the exception of necessary intravenous or subcutaneous injections, should be avoided where possible.

Outpatients should be warned of the haemorrhagic risks in case of possible trauma.

Heparin should be administered with caution to patients with hypertension, a history of ulcers, or with vascular diseases of the chorio-retina, impaired hepatic function, haemostasis disorder, endocarditis, or during surgery of the eyes and central nervous system.

Increased resistance to heparin is frequently encountered with fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in post-surgical patients.

Heparin therapy increases the risk of localised haemorrhage during and following oral surgical (dental) procedures. Temporary heparin dosage reduction or withdrawal may therefore be advisable prior to oral surgery.

Heparin therapy should be monitored carefully. Adequate monitoring of therapy reduces the risk of overdosage and consequent risk of haemorrhage and is an important guide to the development of serious adverse reactions such as delayed onset thrombocytopenia.

Platelet counts should be monitored in patients receiving heparin for more than a few days, since heparin may cause thrombocytopenia with severe thromboembolic complications. Heparin should be discontinued if thrombocytopenia develops.

Patients on heparin may rarely develop heparin-induced thrombosis-thrombocytopenia syndrome (HITTS or "white clot syndrome"): new thrombus formation in association with thrombocytopenia, as a result of irreversible platelet aggregation. This may lead to severe thromboembolic complications such as deep vein thrombosis, cerebral vein thrombosis, limb ischaemia, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possibly death. Heparin administration should therefore be discontinued if a patient develops new thrombosis in association with thrombocytopenia. These effects are probably of immuno-allergic nature, and occur mostly between the fifth and 21st day of treatment in patients being treated with heparin for the first time.

Delayed onset of HIT and HITT

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.

Hyperkalaemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, in patients at risk of increased potassium levels such as patients with diabetes mellitus, renal insufficiency or taking drugs that may increase plasma potassium levels such as ACE inhibitors. The risk of hyperkalaemia appears to increase with the duration of treatment, but is normally reversible.

Heparin resistance

Resistance to heparin is encountered in patients with antithrombin III deficiency. Adjustment of heparin doses based on anti factor Xa levels may be warranted.

Use in hepatic impairment

Heparin should be administered with caution to patients with hepatic disease. Dosage reduction may be necessary in patients with advanced hepatic disease.

Use in renal impairment

Heparin should be administered with caution to patients with renal disease. Dosage reduction may be necessary in patients with advanced renal disease.

Use in the elderly

Dosage should be reduced in elderly people. Patients aged 60 years or over, especially women, may be more susceptible to haemorrhage during heparin therapy. Patients should be carefully monitored.

Paediatric use

See **Section 4.2 – Dose and method of administration** for dosage in children.

Effects on laboratory tests

Significant elevations of AST and ALT levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since AST determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary embolism, rises that might be caused by drugs (like heparin) should be interpreted with caution.

4.5 Interactions with other medicines and other forms of interactions

Heparin may prolong the one-stage prothrombin time. Therefore, when heparin is given with oral anticoagulants such as warfarin, a period of at least 5 hours after the last intravenous dose, or 24 hours after the last subcutaneous dose of heparin, should elapse before blood is drawn for a valid prothrombin time to be obtained.

Medicines which affect platelet function, e.g. aspirin, other salicylates and other non-steroidal anti-inflammatory agents, platelet aggregation inhibitors, glycoprotein IIb/IIIa antagonists, thienopyridines, dextran, dipyridamole and systemic corticosteroids, may increase the risk of haemorrhage and should be used with caution in patients receiving heparin. Where concomitant use cannot be avoided, careful clinical and biological monitoring should be undertaken.

Other medicines which may potentiate the effect of heparin include hydroxychloroquine, sulphinpyrazone, probenecid, ethacrynic acid, vitamin K antagonists, cytostatic agents, cephamandole, cefotetan, plicamycin, valproic acid and propylthiouracil. High doses of penicillins, some contrast media, asparaginase and epoprostenol may also affect the coagulation process and increase the risk of haemorrhage.

Concomitant use of thrombolytic agents such as alteplase, anistreplase, streptokinase or urokinase may also increase the risk of haemorrhage.

Antihistamines, digitalis glycosides, tetracyclines, nicotine, ascorbic acid and quinine may reduce the anticoagulant effect of heparin.

Glyceryl trinitrate has been reported to reduce the activity of heparin when both drugs are administered simultaneously intravenously. This effect may be due to the presence of propylene glycol as a solvent in many glyceryl trinitrate parenteral preparations. No interaction has been reported when the glyceryl trinitrate was administered immediately after the heparin. Adjustment of heparin dosage during and following administration of intravenous glyceryl trinitrate may be required.

Intravenous nitroglycerin, also known as glyceryl trinitrate, administered to heparinised patients may result in a decrease of the partial thromboplastin time with subsequent rebound effect upon discontinuation of nitroglycerin. Careful monitoring of partial thromboplastin time and adjustment of heparin dosage are recommended during co-administration of heparin and intravenous nitroglycerin.

Heavy alcohol drinkers are at greater risk of major heparin associated bleeding than moderate or non-drinkers.

Experimental evidence suggests that heparin may antagonise the actions of ACTH, corticosteroids and insulin.

Heparin is incompatible with certain substances in aqueous solution. Reference to specialised literature should be made to verify in which solution the incompatibility was noted. The following incompatibilities have been reported: hydrocortisone; hyaluronidase; hydroxyzine; some antihistamines, narcotic analgesics, phenothiazines and antibiotics. Refer to **Section 6.2 – Incompatibilities**.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy (Category C†)

The use of heparin in pregnancy has the usual risks for the mother, in particular osteoporosis and thrombocytopenia. Although heparin does not cause malformations, an increased incidence of human foetal loss and prematurity associated with haemorrhage has been reported.

† *Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.*

Use in lactation

Heparin is not distributed into milk and heparin therapy is therefore not contraindicated in women who are breast-feeding. However, administration to breast-feeding women has rarely been reported to cause rapid (within 2 to 4 weeks) development of severe osteoporosis and vertebral collapse.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

4.8 Adverse effects (undesirable effects)

Haemorrhage is the major risk of heparin therapy and may range from minor local ecchymoses to major haemorrhagic complications. An overly prolonged clotting time or minor bleeding can usually be controlled by discontinuing the heparin (see **Section 4.9 – Overdose**). The occurrence of significant gastrointestinal or urinary tract bleeding during heparin therapy may indicate the presence of an underlying occult lesion.

Bleeding can occur at any site, but some specific haemorrhagic complications can be difficult to detect.

a) Adrenal haemorrhage with resultant acute adrenal insufficiency has occurred during anticoagulant therapy. Anticoagulant treatment should be discontinued in patients who develop signs and symptoms of acute adrenal haemorrhage and insufficiency. Plasma cortisol levels should be measured immediately. Corticosteroid therapy should be initiated promptly, before laboratory confirmation of the diagnosis, as any delay in treatment may result in the patient's death.
b) Ovarian (corpus luteum) haemorrhage may be fatal if unrecognised.
c) Retroperitoneal haemorrhage.

Additionally both spinal haematomas and epidural haematomas can occur.

Thrombocytopenia has been reported to occur in up to 30% of patients receiving heparin. Although the thrombocytopenia is often mild and of no obvious clinical significance, it may be accompanied by severe thromboembolic complications such as skin necrosis, gangrene of the extremities, myocardial infarction, pulmonary embolism and stroke (see **Section 4.4 – Special warnings and precautions for use**). Certain episodes of painful, ischaemic and cyanosed limbs have in the past been attributed to allergic vasospastic reactions; however these reactions may instead be complications of thrombocytopenia.

Delayed onset thrombocytopenia is also a possible complication of heparin therapy. If this occurs, the drug should be withdrawn immediately (see **Section 4.4 – Special warnings and precautions for use**).

Skin necrosis has infrequently been reported at injection sites. It is thought to be a localised manifestation of heparin-induced platelet aggregation and thrombosis, and should be taken as a warning sign in patients who develop it. Heparin should be discontinued immediately.

Local irritation, erythema, mild pain, haematoma or ulceration may follow deep subcutaneous injection. The emergence of firm nodules may be noted in some cases; however, these nodules usually disappear after a few days.

Allergic reactions to heparin occur rarely. Hypersensitivity may be manifested by pruritus, urticaria, chills, fever, asthma like symptoms, rhinitis, lacrimation, headache, nausea, vomiting and anaphylactoid reactions, including angioedema and shock. The most common manifestations are urticaria, chills and fever. Itching and burning, especially on the plantar side of the feet, may occur.

Osteoporosis complicated by spontaneous bone fracture has been reported with prolonged use of large doses of heparin.

Alopecia and priapism have occurred rarely in patients treated with heparin.

Hypoaldosteronism.

Suppression of aldosterone synthesis with hyperkalaemia and/or metabolic acidosis have been noted in patients at risk (e.g. diabetes, renal failure).

Suppression of renal functions has occurred following long term, high dose administration of heparin.

Significant elevations of AST and ALT levels have occurred in a high percentage of subjects who have received heparin (see **Section 4.4 – Special warnings and precautions for use: Effects on laboratory tests**).

Hypereosinophilia, which is reversible on discontinuation of heparin treatment, has occurred.

Rebound hyperlipidaemia has been reported following discontinuation of heparin therapy has also been reported.

Transaminases increased.

4.9 Overdose

Symptoms

The main complication associated with heparin overdose is over-anticoagulation and haemorrhage. Examples of types of bleeding observed in patients receiving heparin sodium following subcutaneous administration include melanemia, haematoma, haematuria, ecchymoses, epistaxis, haematemesis, intracranial haemorrhages, pulmonary haemorrhage and other haemorrhage.

Treatment

Slight haemorrhage due to overdosage can usually be treated by withdrawing the drug. Severe bleeding may be reduced by the administration of protamine sulphate. Protamine sulphate should be administered intravenously. To avoid circulatory side effects, the injection should be given slowly over a period of about 10 minutes. Not more than 50 milligrams should be given at any one time. The dose of protamine sulphate required is governed by the amount of heparin that has to be neutralised; approximately 1 milligram of protamine sulphate neutralises 100 units of heparin (mucous) that has been injected in the previous 15 minutes. Since heparin is being continuously excreted, the dose should be reduced as more time elapses after the heparin injection. Ideally, the dose of protamine sulphate required should be accurately determined by titration methods as the antagonist itself, in gross excess, acts as an anticoagulant.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Heparin is a naturally occurring mucopolysaccharide which inhibits the clotting of blood *in vitro* and *in vivo*. It enhances the rate at which antithrombin III neutralises thrombin and activated factor X (Xa). Antithrombin III also neutralises other activated coagulation factors, e.g. factors IX, XI, XII and plasmin.

With low dose heparin therapy, anticoagulation appears to result from neutralisation of Xa which prevents the conversion of prothrombin to thrombin. With full dose heparin therapy, anticoagulation appears to result primarily from neutralisation of thrombin which prevents the

conversion of fibrinogen to fibrin. Full dose heparin therapy also prevents the formation of a stable fibrin clot by inhibiting activation of fibrin stabilising factor.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Heparin is not absorbed from the gastrointestinal tract and must be administered parenterally. Its onset of action is immediate following intravenous administration. There may be considerable variation among patients in the extent of absorption following deep subcutaneous injection of heparin; however, the onset of activity usually occurs within 20 to 60 minutes.

Distribution

Heparin is extensively bound to plasma proteins. It does not cross the placenta and is not distributed into milk.

Metabolism

The metabolic fate of heparin is not fully understood. No biotransformation in plasma or liver, nor any renal excretory mechanism has been identified as primarily responsible for elimination of the drug. It has been suggested that transfer and storage in the reticuloendothelial system may play a role, or that heparin may be partially metabolised in the liver.

Excretion

After administration of large doses intravenously, a small fraction of unchanged drug is excreted in the urine.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium hydroxide

Water for injections

6.2 Incompatibilities

Incompatibility has been reported between heparin (sodium) and alteplase, amikacin sulphate, amiodarone, ampicillin sodium, benzylpenicillin sodium, cephalothin sodium, ciprofloxacin lactate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulphate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulphate, methicillin sodium, netilmicin sulphate, opioid analgesics, oxytetracycline hydrochloride, polymyxin B sulphate, promazine hydrochloride, promethazine hydrochloride, streptomycin sulphate, sulphafurazole diethanolamine, tetracycline hydrochloride, tobramycin sulphate, vancomycin hydrochloride and vinblastine sulphate. Heparin sodium has also been reported to be incompatible with cisatracurium besylate, labetalol hydrochloride and nicardipine hydrochloride. Admixture with glucose can have variable effects. Incompatibility has been reported between heparin and fat emulsion.

6.3 Shelf life

Refer to outer carton for expiration date.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

DBL Heparin Sodium Injection BP is supplied in glass ampoules (bacteriostat free).

Pack size

1,000 IU/1 mL (cartons contain 5 and 50 ampoules)
5,000 IU/1 mL (cartons contain 5 and 50 ampoules)

Not all presentations may be available locally.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physiochemical properties

No data available.

7 NAME AND ADDRESS OF PRODUCT OWNER

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