NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Heparin Sodium (Pfizer) 5000 IU/5mL, 25000 IU/5mL Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule contains Heparin sodium 1000 IU/mL or 5000 IU/mL, in 5mL ampoules

Heparin sodium is a white or almost white powder, moderately hygroscopic, freely soluble in water.

Heparin sodium is a preparation containing the sodium salt of a sulphated glucosaminoglycan present in mammalian tissues. It is prepared from the lungs or from the intestinal mucosae of pigs.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Heparin Injection is a clear, colourless to straw coloured, sterile, preservative-free solution containing Heparin Sodium BP (porcine mucous) in Water for Injections BP.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- prophylaxis and treatment of thromboembolic disorders such as thrombophlebitis, pulmonary embolism, coronary or venous thrombosis and occlusive vascular disease.
- as a low-dose regimen for the prevention of thromboembolic complications arising as a result of cardiac and arterial surgery.
- as an anticoagulant during blood transfusions, extracorporeal circulation, dialysis and other perfusion techniques and in blood samples for laboratory purposes.

4.2 Dose and method of administration

Dose

Heparin Injection contains no antimicrobial agent and is therefore intended for single use only.

Heparin may be given by intermittent intravenous injection, intravenous infusion or deep subcutaneous injection. It should not be given intramuscularly due to the risk of haematoma

formation at the injection site. There is a wide variation between individuals in the dose required to control thromboembolism and heparin dose is usually determined empirically by adjustment according to the results of laboratory tests.

The dosage of heparin sodium should be adjusted according to the patient's coagulation test results. When heparin is given by continuous intravenous infusion, the coagulation time should be determined approximately every 4 hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each injection during the early stages of treatment and at appropriate intervals thereafter. Dosage is considered adequate when the activated partial thromboplastin time (APTT) is 1.5 to 2 times normal or when the whole-blood clotting time is elevated approximately 2.5 to 3 times the control value. After deep subcutaneous (intrafat) injections, tests for adequacy of dosage are best performed on samples drawn 4 to 6 hours after the injections.

When heparin is added to an infusion solution for continuous intravenous administration, the container should be inverted at least 6 times to ensure adequate mixing and prevent pooling of the heparin in the solution.

When an oral anticoagulant of the coumarin (or similar) type is to be administered in patients already receiving heparin sodium, baseline and subsequent tests of prothrombin activity must be determined at a time when heparin activity is too low to affect the prothrombin time. This is about 5 hours after the last IV bolus and 24 hours after the last subcutaneous dose. If heparin is continuously infused by IV, prothrombin time can usually be measured at any time. In converting from heparin to an oral anticoagulant, the oral anticoagulant should be given in the usual initial amount and thereafter prothrombin time should be determined at the usual intervals. To ensure continuous anticoagulation, it is advisable to continue full heparin therapy for several days after the prothrombin time has reached the therapeutic range. Heparin therapy may then be discontinued without tapering.

Surgery of the heart and blood vessels: Patients undergoing total body perfusion for open heart surgery should receive an initial dose of not less than 150 units of heparin sodium per kilogram of body weight. Frequently a dose of 300 units of heparin sodium per kilogram of body weight is used for procedures estimated to last less than 60 minutes; or 400 units per kilogram for those estimated to last longer than 60 minutes.

Adult: (based on 68kg patient)

- **Low-dose prophylaxis of postoperative thromboembolism.** A number of well controlled clinical trials have demonstrated that low-dose heparin prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep vein thrombosis in the legs (as measured by the I-125 fibrinogen technique and venography) and of clinical pulmonary embolism.

  Therapy should be initiated about two hours prior to surgery. The usual dose is 5,000 IU by deep subcutaneous injection, repeated every 8-12 hours for seven days following surgery or until the patient is ambulatory, whichever is longer. It is recommended that injection sites be rotated to prevent formation of haematomas.

  Heparin is given by deep subcutaneous (intrafat, *i.e.* above the iliac crest or abdominal fat layer, arm, or thigh) injection with a fine (25- to 26-gauge) needle to minimise tissue

trauma. A concentrated solution of heparin sodium is recommended. Such prophylaxis should be reserved for patients over the age of 40 who are undergoing major surgery. Patients with bleeding disorders and those having brain or spinal-cord surgery, spinal anaesthesia, eye surgery, or potentially sanguineous operations should be excluded, as should patients receiving oral anticoagulants or platelet-active drugs. The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or post-operatively should be borne in mind. If such bleeding occurs, discontinuance of heparin and neutralisation with protamine sulfate are advisable. If clinical evidence of thromboembolism develops despite low-dose prophylaxis, full therapeutic doses of anticoagulants should be given unless contraindicated. Prior to initiating heparinisation the physician should rule out bleeding disorders by appropriate history and laboratory tests, and appropriate coagulation tests should be repeated just prior to surgery. Coagulation tests values should be normal or only slightly elevated at these times.

- **Treatment of established venous thrombosis or pulmonary embolism.**

  The following regimes may be followed:

  i) *Continuous intravenous infusion:* a bolus dose of 5,000 IU may be given initially followed by an infusion of 20,000-40,000 IU in one litre of 0.9% Sodium Chloride Injection or in any other compatible solution over 24 hours.

  ii) *Intermittent intravenous injection:* an initial dose of 10,000 IU either undiluted or in 50-100mL 0.9% Sodium Chloride Injection followed by 5,000-10,000 IU every four to six hours.

  iii) *Deep subcutaneous injection:* a different site should be used for each injection to prevent the development of massive haematoma. Usual dose is 5,000 IU injected intravenously followed by a subcutaneous injection of 10,000 IU every eight hours or 15,000 IU every 12 hours.

Extracorporeal dialysis: Follow equipment manufacturers' operating directions carefully.

Blood transfusion: The addition of 400 to 600 IU per 100mL of whole blood is usually employed to prevent coagulation. Usually, 7,500 IU of heparin sodium are mixed with 100mL of 0.9% Sodium Chloride Injection and 6 to 8mL of this sterile solution is then added to each 100mL of whole blood.

Laboratory tests*:* Periodic platelet counts, haematocrits, and tests for occult blood in the stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

Laboratory samples: 70 to 150 IU of heparin sodium per 10 to 20mL sample of whole blood is usually employed to prevent coagulation of the sample. Leukocyte counts should be performed on heparinised blood within 2 hours after the addition of the heparin. Heparinised blood should not be used for isoagglutinin, complement, or erythrocyte fragility tests or platelet counts.

Special Populations

Elderly population: Patients over 60 years of age may require lower doses of heparin.

Paediatric Population

The suggested dose is 50 IU/kg body weight initially by intravenous infusion, followed by 100 IU/kg body weight every four hours (according to clotting time) or continuous infusion of 20,000 IU/m^2/24 hours.

4.3 Contraindications

Heparin Injection should not be administered by intramuscular injection because of the increased incidence of haematomas, irritation and pain at the injection site. Heparin is contraindicated in the following conditions:

- known hypersensitivity to heparin or pork products
- history of heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis
- severe thrombocytopenia or patients for whom suitable blood coagulation tests, *e.g.* the whole blood clotting time, partial thromboplastin time etc, cannot be performed at appropriate intervals (for full-dose administration of heparin).
- heparin sodium should not be administered to patients in an uncontrollable active bleeding state (see section 4.4) except when this condition is the result of disseminated intravascular coagulation.

4.4 Special warnings and precautions for use

Haemorrhage

Haemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in haematocrit, a fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a haemorrhagic event. Heparin should be used with extreme caution in conditions in which there is an increased risk of haemorrhage such as:

Gastrointestinal: gastric or duodenal ulcers, continuous tube drainage of the stomach or small intestine.

Cardiovascular: subacute bacterial endocarditis, severe hypertension.

Surgical: during and immediately after (a) spinal tap or spinal anaesthesia, or (b) major surgery, especially those involving the brain, eye or spinal cord.

Haematological: conditions associated with increased bleeding tendencies, such as haemophilia, thrombocytopenia and some vascular purpuras.

The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. Hence in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with antithrombin III (human).

Elderly patients (patients over 60 years of age), particularly women, appear to have a higher risk of haemorrhage and should be carefully monitored.

Other: Patients' conditions such as menstruation, liver disease with impaired haemostasis and renal disease, should be taken into consideration when Heparin is administered.

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.

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

Spinal/Epidural Haematomas

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 the 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.

Thrombocytopenia

The occurrence of thrombocytopenia has been reported in patients receiving heparin, with an incidence of 0% to 30%. Platelet counts should be obtained at baseline and periodically during heparin administration. Thrombocytopenia induced by heparin may be of two types. The first is an acute, but usually mild, fall in platelet count occurring within 1 to 4 days of initiation of therapy. A direct effect of heparin on platelet aggregation appears to be responsible. Mild thrombocytopenia (count greater than 100,000/mm^3) may remain stable or reverse even if heparin is continued. The second type is a delayed onset thrombocytopenia, which has an immunological basis, and is more severe. It usually occurs after 7 to 11 days of heparin although its onset may be more rapid in some patients. It is generally reversible, platelet counts usually begin to return to normal within 4 days of stopping heparin. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100,000/mm^3 or if recurrent thrombosis develops (see **Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis**), the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT)

Heparin-induced Thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as Heparin-induced Thrombocytopenia and Thrombosis (HITT), the so-called "White-Clot Syndrome". Thrombotic events may also be the initial presentation for HITT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm3 or if recurrent thrombosis develops, the heparin product should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Delayed Onset of HIT and HITT

Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis 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.

Skin Necrosis

With subcutaneous administration of heparin, some cases of skin necrosis have been described, sometimes preceded by painful erythematous lesions. In these cases, immediate suspension of the treatment is advised.

Heparin Resistance

Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, in postsurgical patients, and patients with antithrombin III deficiency. Adjustment of heparin doses based on anti Factor Xa levels may be warranted.

Patient Testing

Heparin therapy should be carefully monitored and adjusted to the patient’s coagulation test results. This will reduce the risk of overdosage and consequent haemorrhage. It is also important as a pre-emptory signal to the development of serious adverse effects such as thrombocytopenia. If the coagulation test is unduly prolonged or if haemorrhage occurs, heparin sodium should be discontinued promptly.

Hypersensitivity

As heparin is derived from animal tissues it should be used with caution in patients with a history of allergy as hypersensitivity reactions may occur (see section 4.8).

Hyperkalaemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients with raised plasma potassium or 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 hyperkalemia appears to increase with the duration of treatment, but is normally reversible.

Drug/Laboratory Test Interactions

Hyperaminotransferasemia: Significant elevations of aminotransferase [serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT)] levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs like heparin should be interpreted with caution.

Use in the Elderly

Elderly patients (patients over 60 years of age), particularly women, appear to have a higher risk of haemorrhage and should be carefully monitored (See section 4.2).

Paediatric Population

(See section 4.2.)

4.5 Interaction with other medicines and other forms of interaction

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

Platelet inhibitors: Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine glycoprotein IIb/IIIa antagonists, thienopyridines and others that interfere with platelet-aggregation reactions (the main haemostatic defence of heparinised patients) may induce bleeding and should be used with caution in patients receiving heparin sodium. Where concomitant use cannot be avoided, careful clinical and biological monitoring should be undertaken.

Nitroglycerin: Intravenous nitroglycerin 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 coadministration of heparin and intravenous nitroglycerin.

Agents increasing serum potassium: Since heparin decreases aldosterone production, elevation of serum potassium may occur. Concomitant use of ACE inhibitors, potassium sparing diuretics (*e.g.* spironolactone, triamterene, amiloride) or potassium supplements may lead to significant increases in serum potassium.

Other interactions: Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium. Heparin should be used with caution in patients receiving other drugs such as altepase, streptokinase and urokinase which affect the coagulation process and which may therefore increase the risk of haemorrhage.

Other medicines which may potentiate the effect of heparin include probenecid, ethacrynic acid, vitamin K antagonists, cytostatic agents, cephamandole, 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.

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.

Effect of Heparin on Other drugs

Heparin can increase the effect of oral antidiabetic agents such as sulfonylureas, as well as benzodiazepines (chlordiazepoxide, diazepam, oxazepam) and propranolol.

4.6 Fertility, pregnancy and lactation

Pregnancy - Category C

Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Long-term usage (>3 to 5 months) of therapeutic doses of heparin during pregnancy may increase the risk of osteoporosis. Heparin therapy during the last trimester and immediate postpartum period is associated with a risk of maternal haemorrhage. Heparin sodium should be given to a pregnant woman only if clearly needed.

Breast-feeding

Heparin is not excreted in the breast milk.

Fertility

No reproduction studies in animals have been performed concerning impairment of fertility.

4.7 Effects on ability to drive and use machines

The effect of the heparin on the ability to drive or use machines has not been systematically evaluated. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities. 4.8 Undesirable effects

Haematological: Haemorrhage is the major risk associated with heparin therapy. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug. Gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site, but certain specific haemorrhagic complications may be difficult to detect.

Adrenal haemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who

develop signs and symptoms of acute adrenal haemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.

Ovarian (corpus luteum) haemorrhage developed in a number of women of reproductive age receiving short- or long-term anticoagulant therapy. This complication if unrecognised may be fatal.

Retroperitoneal haemorrhage has occurred.

Spinal and epidural hematomas have occurred.

Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT) and Delayed Onset of HIT and HITT: The occurrence of thrombocytopenia has been reported in patients receiving heparin, with an incidence of 0% to 30%. Although often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications, such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death (see section 4.4). Delayed onset thrombocytopenia has also been reported. If this occurs, drug withdrawal is indicated.

Local irritation: Skin necrosis at the injection site has been reported and is thought to be a local manifestation of heparin induced platelet aggregation and thrombosis. This should be taken as a warning sign in patients who develop it and heparin therapy should be immediately discontinued. Local irritation, erythema, mild pain, haematoma, or ulceration may follow deep subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.

Hypersensitivity: Generalised hypersensitivity reactions have been reported, with chills, fever, and urticaria as the most usual manifestations. Asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions (including shock) occur more rarely. Itching and burning, especially on the plantar site of the feet, may occur.

Miscellaneous: Osteoporosis following long-term administration of high doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, hyperkalaemia (due to aldosterone suppression), delayed transient alopecia, priapism, and rebound hyperlipidaemia on discontinuation of heparin sodium have also been reported.

Significant elevations of aminotransferase (SGOT and SGPT) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.

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

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

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

The usual sign of overdosage is bleeding or haemorrhage. Nosebleeds, blood in urine or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Treatment

The drug should be withdrawn and clotting time and platelet count should be determined. Prolonged clotting time will indicate that there is an anticoagulant effect requiring neutralisation and in this case, protamine sulfate should be administered. The dose should be calculated by titration of the individual patient's requirements but as a general guide, approximately 1mg of protamine sulfate neutralises 100 IU of heparin (mucous) that has been injected in the previous 15 minutes. No more than 50mg should be administered, very slowly, in any 10 minute period. Since heparin is being continuously eliminated the dose should be reduced as time elapses. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about half an hour after intravenous injection.

Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information the labelling of Protamine Sulfate Injection should be consulted.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group**:** Anticoagulant.

ATC Code: B01AB01

Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, possessing anticoagulant properties. It is composed of polymers of alternating derivations of α-D-glucosamido (*N*-sulfated *O*-sulfated or *N*-acetylated) and *O*-sulfated uronic acid (α-L-iduronic acid or β-D-glucuronic acid).

Heparin CAS Registry Number is 9005-49-6**.**

Mechanism of Action

Heparin is a naturally occurring mucopolysaccharide with *in vitro* and *in vivo* anticoagulant activity. Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. Heparin acts at multiple sites in the normal coagulation

system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilising factor.

5.2 Pharmacokinetic properties

The anticoagulant action is immediate following intravenous injection and is effective for three to six hours. Following deep subcutaneous injection absorption is variable among patients, although onset of activity is between 20 and 60 minutes. Heparin is extensively bound to plasma proteins. It does not cross the placenta and is not excreted in breast milk.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases, it is not measurably affected by low doses of heparin.

Patients over 60 years of age, following similar doses of heparin, may have higher plasma levels of heparin and longer activated partial thromboplastin times (APTTs) compared with patients under 60 years of age.

Peak plasma levels of heparin are achieved 2 to 4 hours following subcutaneous administration, although there are considerable individual variations. Log linear plots of heparin plasma concentrations with time for a wide range of dose levels are linear, which suggests the absence of zero order processes. Liver and the reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10minutes) and, after the age of 40, a slower beta phase indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin. The half-life may be slightly prolonged in renal impairment, decreased in patients with pulmonary embolism, and either increased or decreased in patients with liver disorders. Heparin is excreted in the urine, mainly as metabolites although, following administration of large doses, up to 50% may be excreted unchanged.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

5.3 Preclinical safety data

Genotoxicity

No reproduction studies in animals have been performed concerning mutagenesis.

Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of heparin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid,
Sodium hydroxide,
Water for injections.

6.2 Incompatibilities

Heparinised Saline Injection is incompatible with certain substances in solution. Specialised literature should be consulted to verify with which substances incompatibilities have been noted. The following incompatibilities have been reported: amikacin sulfate, erythromycin lactobionate, gentamicin sulfate, kanamycin sulfate, tetracycline sulfate, tobramycin sulfate, vancomycin hydrochloride, hydrocortisone sodium succinate, doxorubicin, droperidol, ciprofloxacin, mitozantrone, morphine sulfate, haloperidol lactate, promethazine hydrochloride, codeine phosphate, hyaluronidase, benzylpenicillin sodium, methadone hydrochloride, pethidine hydrochloride, reteplase, methicillin sodium, levorphanol bitartrate, alteplase, amiodarone hydrochloride, ampicillin sodium, aprotinin, cephalothin sodium, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, netilmicin sulfate, oxytetracycline hydrochloride, polymyxin B sulfate, streptomycin sulfate, some phenothiazines and vinblastine sulfate.

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

Heparin Injection 5,000IU/5mL: 24 months

Heparin Injection 25,000IU/5mL: 36 months

6.4 Special precautions for storage

Store at or below 25ºC.

6.5 Nature and contents of container

Heparin Injection 5,000IU/5mL Steriluer® plastic ampoule (50s)

Heparin Injection 5,000IU/5mL Steriluer® plastic ampoule (10s)

Heparin Injection 25,000IU/5mL Steriluer® plastic ampoule (50s)

6.6 Special precautions for disposal

Single use only. Discard unused portion.

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

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

27 August 2009

10. DATE OF REVISION OF THE TEXT

29 December 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Safety information updated under the following subheadings: Skin Necrosis Heparin Resistance Hyperkalaemia
4.5	Safety information added to the following subheadings: Platelet inhibitors Other interactions Effect of Heparin on Other drugs
4.7	Safety information regarding driving and handling machinery updated
4.8	Additional Adverse events added throughout section 4.8