AUSTRALIAN PRODUCT INFORMATION – HEPARIN INTERPHARMA (HEPARIN SODIUM) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Heparin Sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 5,000 IU heparin sodium from porcine intestinal mucosa.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Clear, colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prophylaxis and treatment of deep vein thrombosis for use in patients 18 years and older.

4.2 DOSE AND 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.

A guide to dosage schedules for prophylaxis and treatment is presented in Table 1.

Table 1. Suggested Dosage Schedule for Prophylaxis and Treatment with Heparin Sodium

Method of Administration	Frequency	Recommended Dose#
Prophylaxis:	Subcutaneous Heparin Sodium	
Deep, subcutaneous (Intra-fat) injection. A different site should be used for each injection to prevent the development of haematoma	Initial dose	5,000 units by SC injection, Approximately 2 hours pre-operatively followed by maintenance dose
	Maintenance dose	Post-operatively 5,000 units by SC injection, Every 8 to 12 hours until patient mobilises or until adequate vitamin K antagonist activity

Treatment:	Intravenous Heparin Sodium	
Intermittent intravenous injection*	Initial dose	10,000 units
	Maintenance dose	5,000 to 10,000 units Every 4 to 6 hours
Continuous intravenous infusion*	Initial dose	5,000 IU bolus dose
	Maintenance dose	followed by a continuous infusion of at least 30,000 IU for the first 24 h
Weight-adjusted IV regimen	Initial dose	80 IU/kg bolus dose,
	Maintenance dose	followed by 18 IU/kg/h
Intravenous injection then deep, subcutaneous (Intra-fat) injection. A different site should be used for each injection to prevent the development of haematoma	Initial dose	5,000 units injected IV, followed by maintenance dose
	Maintenance dose	10,000 units SC Every 8 hours or 15,000 units SC Every 12 hours
* The prefilled syringe is suitable for substances to be administered intravenously. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems.		
Source: Adapted from DBL Heparin Sodium Injection, Product Information – Australia, Pfizer, 09 March 2021; B.Braun Product Information, Summary of Product Characteristics, Heparin Sodium Injection PFS, 5,000 IU/ 0.5 mL Gresele et al (2012) Heparin in the prophylaxis and Treatment of Thrombosis. In: Lever et al. (eds.), Heparin - A Century of Progress, Handbook of Experimental Pharmacology 207, DOI 10.1007/978-3-642-23056-1_9, # Springer-Verlag Berlin Heidelberg 2012		

Laboratory Monitoring for Efficacy and Safety

Adjust the dosage of HEPARIN INTERPHARMA according to the patient's coagulation test results. 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 injections, tests for adequacy of dosage are best performed on samples drawn 4 to 6 hours after the injections.

Periodic platelet counts and haematocrits are recommended during the entire course of HEPARIN INTERPHARMA therapy, regardless of the route of administration.

Use in hepatic impairment

Dose adjustment may be needed in patients with hepatic impairment. See also Section 4.4 Special warnings and precautions for use.

Use in renal impairment

Dose adjustment may be needed in patients with renal impairment. See also Section 4.4 Special warnings and precautions for use.

Use in the elderly

Dose requirements for heparin might be adjusted in the elderly (patients aged 60 years and over) depending on their individual condition (e.g. kidney function). (See also Section 5.2 Pharmacokinetic properties).

Smokers

Depending on the amount of nicotine present in the body dose adjustments might be necessary. Refer also to Section 4.5 Interactions with other medicines and other forms of interactions.

Obese patients

Clinical trials suggest that in order to provide sufficient anti-coagulation in morbidly obese patient's dose adjustment of heparin might be needed. However no specific dosage recommendations can be made.

Contains no antimicrobial agent. This is for single use only in a single patient. Any residue should be discarded.

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;
- with an uncontrollable active bleeding state (see Section 4.4 Special warnings and precautions for use), except when this is due to disseminated intravascular coagulation.
- 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 (type II) 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.

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.

Heparin may lead to an increase and prolongation of menorrhagia. In case of unusual strong or acyclic uterine bleeding, any organic disease requiring specific treatment should be excluded by a supplementary gynaecological examination.

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, hemostasis 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.

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

After prolonged administration, osteoporosis may develop, especially in predisposed patients (i.e. older people - especially postmenopausal women, pregnant and breastfeeding women). See also Sections 4.6 and 4.8.

Oral Surgery

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.

Serum transaminase

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.

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**.**

Monitoring during treatment

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.

Heparin-induced Thrombosis-Thrombocytopenia Syndrome (HITTS or "white clot syndrome")

Patients on heparin may rarely develop Heparin-induced Thrombosis-Thrombocytopenia Syndrome: new thrombus formation in association with thrombocytopenia, as a result of irreversible platelet aggregation. This may lead to severe thromboembolic complications such as skin necrosis, gangrene of the extremities, myocardial infarction, pulmonary embolism and stroke. 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.

Hyperkalemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, 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 hyperkalemia appears to increase with the duration of treatment, but is normally reversible.

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

There are no adequate and well controlled studies on heparin use in paediatric patients**.** HEPARIN INTERPHARMA is in a prefilled syringe and should not be administered to children since it does not allow a dose adjustment

Effects on laboratory tests

No data available.

4.5 .INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Enhancement of the heparin effect

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.

Weakening of the heparin effect

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.

Alcohol:

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

Nicotine abuse:

Nicotine may increase the clearance of heparin and therefore partially counteracts the anticoagulant effect of heparin. See also Section 4.2 Dose and method of administration.

Influence of heparin on the effect of other drug substances:

Drugs that lead to an increase of the serum potassium level (e.g. aliskiren, ACE inhibitors) should only be administered together with heparin under careful monitoring. See also Section 4.4 Special warnings and precautions for use.

Heparin is known to activate plasma lipoprotein lipase, which should be taken into consideration when heparin is administered concomitantly together with drugs with known high plasma protein binding and narrow therapeutic width (e.g. cardiac glycosides).

Incompatibility

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).

Intravenous nitroglycerin administered to heparinized 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies to evaluate the effects of heparin on fertility and embryonic development have not been conducted in animals.

Use in Pregnancy(Category C)

Animal reproduction studies have not been conducted with heparin sodium.

Unfractionated heparin sodium is not known to cross the placenta. Whilst the possibility of fetal harm or effect on reproduction cannot be excluded, a direct fetal effect is unlikely.

During pregnancy, complications resulting from underlying illness and/or therapy cannot be excluded. Long-term administration (>3 to 5 months)of heparin may increase the risk of osteoporosis in pregnant women (see also Section 4.4 Special warnings and precautions for use).

The tendency for skin lesions is higher in pregnant women compared to non-pregnant women (see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).

For the use of heparin in epidural anaesthesia during labour (see Section 4.4 Special warnings and precautions for use).

For imminent abortion see also Section 4.3 Contraindications.

Use in Lactation.

Heparin- is not excreted in breastmilk. Long-term administration of heparin may increase the risk of osteoporosis in breast-feeding women (see also Section 4.4 Special warnings and precautions for use).

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequent undesirable effects are bleeding events from any organ or tissue.

Besides this, local reactions at the site of administration may occur.

Heparin-induced thrombocytopenia of type II occurs rarely (≥ 1/10,000 to < 1/1,000) but this adverse reaction may become serious. It is assumed to be a hypersensitivity reaction mediated by specific antibodies. For details see below.

Other undesirable effects may include local or systemic allergic reactions.

Undesirable effects are listed according to their frequencies as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)

Not known (Frequency cannot be estimated from the available data).

All reactions that are derived from post-marketing experience (spontaneous reports and literature) only are based on a patient population which is largely unknown. Therefore exact incidences cannot be provided and are referred to with the frequency 'not known'.

Table 2 Adverse events according to System Organ Class and Frequency

System Organ Class	Frequency	Event
Blood and lymphatic system disorders	Common	*Heparin-induced thrombocytopenia type I* At the beginning of heparin therapy mild heparin-induced thrombocytopenia type I (platelet count 100,000 – 150,000 per microlitre), without thrombosis. The thrombocytopenia usually occurs within the first 5 days of administration, and is probably due to a direct effect on platelets 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.
	Unknown	Eosinophilia. Hypereosinophilia, which is reversible on discontinuation of heparin treatment, has occurred.

System Organ Class	Frequency	Event
Skin and subcutaneous tissue disorders	Uncommon	Transient alopecia following long-term administration, skin necrosis
Musculoskeletal and connective tissue disorders	Not known	Osteoporosis (after long-term administration of heparin) (see also Sections 4.4 Special warnings and precautions for use and 4.6 Fertility, pregnancy and lactation).
Endocrine disorders	Rare	Hypoaldosteronism, resulting in hyperkalaemia and metabolic acidosis, especially in patients with impaired kidney function and diabetes mellitus. See also Section 4.4 Special warnings and precautions for use.
	Not known	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.

System Organ Class	Frequency	Event
Vascular disorders	Very common	Haemorrhage; see also Sections 4.4 Special warnings and precautions for use and 4.9 Overdose. Depending on the dose, increased incidence of bleeding from any organ or tissue. 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.
	Not known	Ovarian (corpus luteum) haemorrhage - may be fatal if unrecognised. Retroperitoneal haemorrhage. Both spinal hematomas and epidural hematomas can occur
	Very rare	Vasospasm
General disorders and administration site conditions	Common	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. Local tissue reactions at the injection site, such as induration, redness, discolouration, and minor haematomas 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.
Immune system disorders	Uncommon	Allergic reactions of all types and severities, with various manifestations (e.g. urticaria, pruritus, dyspnoea, bronchospasm, hypotension).
	Rare	Severe heparin-induced, antibody-mediated thrombocytopenia (Heparin-induced thrombocytopenia type II, for details see below)
	Very rare	Anaphylactic shock especially in sensitized patients having previously received heparin Onset of type II thrombocytopenia with a delay of up to several weeks after the end of heparin administration.

System Organ Class	Frequency	Event
	Not known	Type IV hypersensitivity reaction (e. g. skin lesions, erythematous papules and plaques located at injection site) which may occur with a latency of up to several months. Hypersensitivity may be manifested by pruritus, urticaria, chills, fever, asthma like symptoms, rhinitis, lacrimation, headache, nausea, vomiting and anaphylactoid reactions, including angioedema and shock.
Hepatobiliary disorders	Very common	Hepatic enzymes increased (increases of the serum concentrations of transaminases (AST, ALT), gamma-glutamyl transpeptidase, lactate dehydrogenase and lipase, possible resulting in increased free fatty acids). These reactions are, however, reversible
Reproductive system and breast disorders	Very rare	Priapism

Information on particular undesirable effects

Heparin induced thrombocytopenia type II

Severe heparin-induced, antibody-mediated thrombocytopenia (type II thrombocytopenia, HIT II), is characterised by platelet counts markedly below 100 000 per microlitre or a rapid decrease to less than 50 per cent of the initial value and accompanied by arterial or venous thromboses or embolism, consumption coagulopathy, skin necroses at the site of injection. The anticoagulatory effect of heparin may be reduced.

In patients without pre-existing hypersensitivity to heparin the decrease of the platelet count typically begins between 5 to 14 days after commencement of the heparin therapy. In patients with existing antibodies to heparin such decrease may begin already after a few hours. The greater the degree of trauma and thus the release of PF4, the more likely patients went on to develop HIT antibodies and clinical HIT.

As soon as type II thrombocytopenia occurs, heparin administration must be discontinued immediately. Emergency treatment depends on the nature and severity of the symptoms. Re-exposure of the patient to parenteral heparin is absolutely contraindicated.

Patients undergoing extracorporeal circulation.

Principally the same ADRs that occur in other patients might occur. Haemodialysis patients might be at an increased risk for developing anaphylactic or anaphylactoid reactions.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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

Mild symptoms

Slight haemorrhage due to overdosage can usually be treated by withdrawing the drug.

Severe symptoms

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Anti-thrombotic agents, heparin group, ATC code B01A B01.

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

The safety and efficacy of unfractionated heparin has been demonstrated by decades of use in the clinic.

The safety and efficacy of HEPARIN INTERPHARMA was assessed in a single dose cross over comparison with a foreign registered product in healthy adults. A total of 10 adverse events were reported by 7 (23%) of the 30 subjects who participated in this study. All of the AEs were mild (9/10; 90%) or moderate (1/10, 10%) in severity. No severe AEs, deaths or withdrawals were reported.

Studies published in the literature and post-market surveillance data have not identified new safety concerns for heparin sodium.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Because of its high relative molecular mass and its negative surface charge heparin is not absorbed from the intestine. Intake by the parenteral route intravenous or subcutaneous is used. Intake by inhalation is possible.

Once administered subcutaneous heparin follows non-linear kinetics, as there is a combination of saturable and non-saturable mechanisms of clearance. This effect thereby reduces the unbound fraction of heparin and also heparin's anticoagulant activity at low concentrations. Additionally, binding of heparin to Von-Willebrand- factor inhibits platelet function. The bioavailability of subcutaneously administered heparin is dose-dependent. The bioavailability of the anti-factor Xa activity increases with the dose delivered and tends from approximately 30 % with low doses toward 100 % at high doses. Therefore after subcutaneous injection, the onset of the heparin effect is delayed for approximately 0.5 - 1 hour after administration.

Distribution

Heparin is strongly bound to plasma proteins (LDL, globulins, in particular AT and fibrinogen). Therefore the distribution volume is generally limited to the plasma volume. This is also valid for adults undergoing dialysis; here the volume of distribution has been reported to be approximately 0.07 L/kg.

Metabolism

The saturable phase of heparin clearance is attributed to binding to the reticulo-endothelial system (e.g. endothelial cell receptors, macrophages), where it is internalized and depolymerised followed by its degradation in the liver by heparinises and urinary excretion mainly in the form of depolymerized inactivated heparin.

Excretion

After parenteral administration heparin is eliminated from the blood through a combination of rapid saturable mechanism of zero-order and much slower first-order mechanism. The interindividual half-life has been reported to be approximately 1 - 2 hours. It depends on the actual dose administered, on liver and kidney function and on accompanying diseases

5.3 PRE-CLINICAL SAFETY DATA

Nonclinical data sourced from published literature reveal no special hazard for humans based on conventional data of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, toxicity to reproduction and development.

In animal studies only effects have been observed that have already been described also for humans in Section 4.8 Adverse effects (Undesirable effects), such as osteoporosis and bleeding.

Genotoxicity

In vitro data suggest heparin is associated with DNA inhibition, unscheduled DNA synthesis, and unspecified DNA damage in various bacterial and mammalian cell types. No in vivo data are available.

Carcinogenicity

No studies in animals have been performed to evaluate the carcinogenic potential of heparin sodium.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Water for injections
- Sodium hydroxide (for pH adjustment)
- Hydrochloric acid (for pH adjustment)

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, netilimicin 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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate or freeze.

Only use the product if the solution is clear and the container is intact. Do not use if solution is yellow or contains precipitates.

6.5 NATURE AND CONTENTS OF CONTAINER

HEPARIN INTERPHARMA is supplied in ready to use type I clear glass prefilled syringes containing 0.5 mL sterile solution for injection. Each syringe is provided with an affixed siliconised 27g x ½" stainless steel needle with a needle shield.

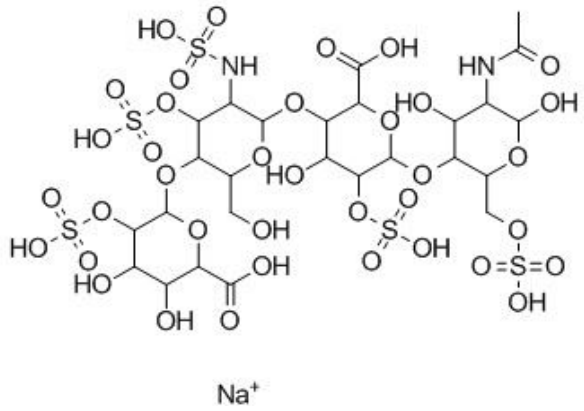
Pack size – 10 x prefilled syringe

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

9041-08-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - (Prescription only medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

TBA

10 DATE OF REVISION