AUSTRALIAN PRODUCT INFORMATION – HEPARINISED SALINE (HEPARIN SODIUM) SOLUTION FOR INJECTION

1. NAME OF THE MEDICINE

Heparin sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparinised Saline Injection is a clear, colourless, sterile, preservative-free solution containing 50 IU/5mL Heparin Sodium (porcine mucous).

3. PHARMACEUTICAL FORM

Heparinised Saline Injection is a clear, colourless solution, free from visible impurities.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- maintenance of the patency of intravenous injection devices

4.2 Dose and Method of Administration

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

To maintain the patency of intravenous injection devices and prevent clot formation, flush the catheter/cannula with 10 – 50 IU every four hours. The solution may be used following initial placement of the device in the vein, after each injection of a medication, or after withdrawal of blood for laboratory tests. If the drug to be administered is incompatible with Heparin (see Section 4.5 Interactions With Other Medicines and Other Forms of Interaction), the device must be flushed through with normal 0.9% Sodium chloride solution before and after the drug is administered. When heparin would interfere with or alter the results of blood tests, the heparin solution should be cleared from the device by aspirating and discarding it before withdrawing the blood sample. Consult the device manufacturer's instructions for specific details.

Note: Since repeated injections of small doses of heparin can alter tests for activated partial thromboplastin time (APTT), a baseline value for APTT should be obtained prior to insertion of an intravenous device.

4.3 Contraindications

- known hypersensitivity to heparin or pork products,
- heparinised saline should not be used for anticoagulant therapy,
- severe thrombocytopenia,

- History of heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis,

- heparin sodium should not be administered to patients in an uncontrollable active bleeding state (see Section 4.4 Special Warnings and Precautions for Use) except when this condition is the result of disseminated intravascular coagulation.

4.4 Special Warnings and Precautions for Use

Heparin is not intended for intramuscular use.

- Heparinised Saline Injection is not recommended for use in neonates.

- In infants, the cumulative amounts of heparin received from frequent administration of Heparinised Saline Injection during a 24-hour period should be considered.

- Precautions must be exercised when drugs, which are incompatible with heparin, are administered through an indwelling intravenous catheter containing Heparinised Saline Injection (see Section 4.5 Interactions With Other Medicines and other forms of interactions).

- **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 warrants consideration of a haemorrhagic event. Heparin should be used with 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: actual or potential haemorrhagic states, such as haemophilia, thrombocytopenia and some vascular purpuras.

  Elderly patients, particularly women, appear to have a higher risk of haemorrhage and should be carefully monitored.

  Other: menstruation, liver disease with impaired haemostasis and renal disease.

- **Thrombocytopenia**: Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0% to 30%. Platelet counts should be obtained at baseline and periodically during heparin administration. Mild thrombocytopenia (count greater than 100,000/mm^3) may remain stable or reverse even if heparin is continued. 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), heparin 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.

- **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.

- **Laboratory tests:** Periodic platelet counts, haematocrits and tests for occult blood in stools are recommended during the entire course of heparin use.

Use in the elderly

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

Paediatric use

Heparinised Saline Injection is not recommended for use in neonates.

Effects on laboratory tests

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 therapy, although the low dose of Heparinised Saline would not normally evoke this.

4.5 Interactions with Other Medicines and Other Forms of Interactions

- **Platelet inhibitors:** Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine, 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.

- **Other interactions:** Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium.

- 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 of heparin sodium.

- 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.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

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

Use in pregnancy - Category C

Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Use in lactation

Heparin is not excreted in the breast milk.

4.7 Effects on Ability to Drive and Use Machines

4.8 Adverse Effects (Undesirable Effects)

- *Haematological:* Haemorrhage is the major risk associated with heparin therapy although the low dose of Heparinised Saline would not normally evoke this. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug.

- *Hypersensitivity:* Heparin in therapeutic and prophylactic doses is essentially non-toxic but may cause allergic reactions and possibly anaphylactic reactions in susceptible patients. Generalised hypersensitivity reactions have been reported, with chills, fever, and urticaria as the most common manifestations; asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions (including shock) have occurred more rarely. Itching and burning, especially on the plantar site of the feet, may occur.

- *Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT) and Delayed Onset of HIT and HITT:* 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 and which may resolve without cessation of treatment. A direct effect of heparin on platelet aggregation appears to be responsible. The second type is a delayed onset thrombocytopenia, which has an immunological basis, and is more serious. It usually occurs after 7 to 11 days of heparin and drug withdrawal is indicated.

Thrombocytopenia of any degree should be monitored closely (see Section 4.4 Special Warnings and Precautions for Use).

- *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 and erythema have been also been reported.

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 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 50 mg 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.

Protamine may cause anaphylactoid reactions that may be life threatening. (See the protamine label for additional information). Hence the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of drug: Anticoagulant

Mechanism of action

Heparin is a naturally occurring mucopolysaccharide with *in vitro* and *in vivo* anticoagulant activity. Heparin acts at multiple sites in the normal coagulation systems. 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, which in turn prevents the conversion of fibrinogen to fibrin. Under normal conditions an equilibrium between fibrinogen deposition and lysis keeps the vascular system free of thrombi. Under abnormal conditions of trauma, surgery or circulatory collapse, the equilibrium shifts towards clot formation. The action of heparin is to shift the equilibrium back towards normal thereby reducing clot formation.

Clinical trials

5.2 Pharmacokinetic Properties

Heparin is extensively bound to plasma proteins. It does not cross the placenta and is not excreted in breast milk. The exact route of metabolism of heparin is unknown and well defined renal elimination of the drug has not been identified. In the absence of evidence for a conventional route of elimination, transfer to an extravascular space such as the reticuloendothelial system has been postulated.

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.

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 reticuloendothelial 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 indicate 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.

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 Chloride

Sodium hydroxide

Water for Injection

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, streptomycin 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

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 25ºC. Single use only. Discard unused portion.

6.5 Nature and Contents of Container

AUST R 66684: Heparinised Saline Injection 50 IU/5mL (sterile) Steriluer® (50s) is supplied in an LDPE ampoule.

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

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 sodium is a preparation containing the sodium salt of a sulphated glucosaminoglycan present in mammalian tissues. It is prepared from the intestinal mucosae of pigs. Heparin sodium is a white or almost white powder, moderately hygroscopic, freely soluble in water.

CAS number

9005-49-6.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Medicine)

8. SPONSOR

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9. DATE OF FIRST APPROVAL

27 October 1998

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20 August 2019

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Summary Table of Changes

Section changed	Summary of new information
All	Reformat in line with the new form
1; 2; 5; 6; 7; 9; 10	Editorial changes
2	Add quantitative information
3	Add visual identification details
6.1	Add excipients
8	Update sponsor details