1 HEPARIN SODIUM (2U/mL solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance
Heparin sodium (2U/mL).

The biological origin of the active substance
Heparin is a heterogeneous mixture of variably sulphated polysaccharide chains composed of repeating units of disaccharides, D-glucosamine and L-iduronic acid or D-glucosamine and D-glucuronic acids. It is extracted from porcine intestinal mucosa.

Upon complete hydrolysis, it yields a mixture of D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulphuric acid.

Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes.

Excipient with known effect
Sodium chloride (0.9%).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

HEPARIN SODIUM intravenous infusion is a sterile, non-pyrogenic solution of heparin sodium (BP) standardised for use as an anticoagulant in 0.9% Sodium Chloride intravenous infusion buffered with 0.4mg citric acid monohydrate and 5.8mg sodium phosphate-dibasic dodecahydrate (Na₂HPO₄ 12 H₂O) per mL to pH range of 5.5 - 8.0.

Heparin is strongly acidic because of its content of covalently linked sulphate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulphate units are partially replaced by sodium ions.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

HEPARIN SODIUM solution for intravenous infusion is indicated as an anticoagulant in extracorporeal circulation, dialysis procedures, and as an aid in the maintenance of catheter patency.

4.2 Dose and method of administration

HEPARIN SODIUM is not effective by oral administration and should not be given orally.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Use of a final filter is recommended during administration of all parenteral solutions, where possible.

Do not administer unless solution is clear and seal is intact.
Use in extracorporeal therapy
The concentration of 2 units/mL will suffice to prevent clotting on initiation of extracorporeal therapy by priming the devices with this solution. NOTE: A proper and effective heparinisation schedule must be initiated in the patient before and maintained throughout the procedures to prevent subsequent clotting and blood path obstruction. The particular manufacturer’s directions for use of the dialyser or other extracorporeal apparatus must be referred to. The direction sheets for the use of therapeutic dosage forms of heparin must equally be referred to and adjusted to a given patient's condition and response to achieve sustained, effective anticoagulation within clinically safe parameters. Both intermittent and continuous infusion of 5000, 10000 or 20000 units are employed for this purpose and are unrelated to the low dose heparin in this preparation that is directed at preparing the apparatus for initial use.

Maintenance of catheter patency
Although the rate for infusion of the 2 units/mL formulation is dependent upon age, weight, clinical condition of the patient and the procedure being employed, an infusion rate of 3 mL/hour has been found to be satisfactory.

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

All injections in VIAFLEX plastic containers are intended for administration using sterile equipment. It is recommended that the intravenous administration apparatus be replaced at least every 24 hours.

Because dosages of this drug are titrated to response, no additives should be made to HEPARIN SODIUM Injection.

4.3 Contraindications
HEPARIN SODIUM should not be used in the following patients:
- With known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- With severe thrombocytopenia;
- In whom suitable blood coagulation tests - e.g. the 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);
- With an uncontrollable active bleeding state (see Section 4.4), except when this is due to disseminated intravascular coagulation.

4.4 Special warnings and precautions for use
White Clot syndrome
It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets induced by heparin, the so-called “white clot syndrome”. The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possible death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

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 medicines 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 patient's anticoagulated or to be anticoagulated for thromboprophylaxis.

**Heparin resistance**

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

**Haemorrhage**

Haemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in haematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of haemorrhagic event.

**HEPARIN SODIUM** should be used with extreme caution in disease states in which there is increased danger of haemorrhage. Some of the conditions in which increased danger of haemorrhage exists are:

- **Cardiovascular**: Subacute bacterial endocarditis. Severe hypertension.
- **Surgical**: During and immediately following (a) spinal tap or spinal anaesthesia or (b) major surgery, especially involving the brain, spinal cord or eye.
- **Haematologic**: Conditions associated with increased bleeding tendencies, such as haemophilia, thrombocytopaenia, and some vascular purpuras.
- **Gastrointestinal**: Ulcerative lesions and continuous tube drainage of the stomach or small intestine.
- **Other**: Menstruation, liver disease with impaired hemostasis.

**Coagulation testing**

When **HEPARIN SODIUM** is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if haemorrhage occurs, **HEPARIN SODIUM** should be discontinued promptly (see Section 4.9).

**Thrombocytopaenia**

Thrombocytopaenia 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 thrombocytopaenia (count greater than 100,000/mm$^3$) may remain stable or reverse even if heparin is continued. However, thrombocytopaenia of any degree should be monitored closely. If the count falls below 100,000/mm$^3$ or if recurrent thrombosis develops (see HIT and HITT below), the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.

Solutions containing sodium ions should be used with great care in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there exists oedema with sodium
retention. These solutions should also be used with caution in patients receiving corticosteroids or
corticotropic.

The intravenous administration of solutions can cause fluid and/or solute overloading resulting in
dilution of serum electrolyte concentrations, over hydration, congested states or pulmonary
oedema. The risk of dilutional states is inversely proportional to the electrolyte concentrations and
volume of the infusion. The risk of solute overload causing congested states with peripheral and
pulmonary oedema is directly proportional to the electrolyte concentrations and volume of the
infusion.

Excessive administration of potassium free solutions may result insignificant hypokalaemia.

In patients with diminished renal function, administration may result in sodium retention.

*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).
Thrombotic events may also be the initial presentation of 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.

Once HIT or HITT is diagnosed or strongly suspected, all heparin sodium sources (including heparin
flushes) should be discontinued and an alternative anticoagulant used. Future use of heparin
sodium, especially within 3 to 6 months following the diagnosis of HIT or HITTs, and while patients
test positive for HIT antibodies, should be avoided.

Immune-mediated HIT is diagnosed based on clinical findings supplemented by laboratory test
confirming the presence of antibodies to heparin sodium, or platelet activation induced by heparin
sodium. A drop in platelet count greater than 50% from baseline is considered indicative of HIT.
Platelet counts begin to fall 5 to 10 days after exposure to heparin sodium in heparin-naive
individuals, and reach a threshold by days 7 to 14. In contrast, ‘rapid onset’ HIT can occur very
quickly (within 24 hours following heparin sodium initiation), especially in patients with a recent
exposure to heparin sodium (i.e. previous 3 months). Thrombosis development shortly after
documenting thrombocytopenia is a characteristic finding in almost half of the patients.

Thrombocytopenia of any degree should be monitored closely. If the platelet counts fall below
100,000/mm$^3$ or if recurrent thrombosis develops, the heparin product should be promptly
discontinued and alternative anticoagulant considered if patients require continued anticoagulation.

*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.

*Laboratory tests*

Periodic platelet counts; hematocrits, and tests for occult blood in stool are recommended during
the entire course of heparin therapy, regardless of the route of administration (see Section 4.2).
**Use in elderly**
A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age (see Section 4.4/Haemorrhage). Clinical studies indicate that lower doses of heparin may be indicated in these patients.

**Paediatric use**
Safety and effectiveness in paediatric patients has not been established.

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**
Medicines 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.

**Drug/Laboratory tests interactions**
**Hyperaminotransferaseaemia:** Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) 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 medicines (like heparin) should be interpreted with caution.

4.6 Fertility, pregnancy and lactation

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

**Pregnancy (Category C)**
Heparin does not cross the placental barrier. Animal reproduction studies have not been conducted with HEPARIN SODIUM. It is 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 pregnant women only if clearly needed.

**Breast-feeding**
Heparin is not excreted in human milk.

4.7 Effects on ability to drive and use machines
Not applicable.
4.8 Undesirable effects

Haemorrhage

Haemorrhage is the chief complication that may result from heparin therapy (see Section 4.4). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see Section 4.9). It should be appreciated that 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 haemorrhage complications may be difficult to detect:

a) 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 a patient's death.

b) 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.

c) Retroperitoneal haemorrhage.

Local irritation

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

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

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 - 30%. While 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 possible death (see Section 4.4/Thrombocytopenia, Heparin-induced Thrombocytopenia(HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT)).

Certain episodes of painful, ischaemic, and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia-associated complications remains to be determined.

Miscellaneous

Osteoporosis following long term administration of high doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipaemia on discontinuation of heparin sodium have also been reported. Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received 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**
Bleeding is the chief sign of heparin overdosage. 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**

*Neutralization of heparin effect:* When clinical circumstances (bleeding) require reversal of heparinisation, protamine sulphate (1% solution) by slow infusion will neutralise **HEPARIN SODIUM**. No more than 50mg should be administered, very slowly in any 10-minute period. Each mg of protamine sulphate neutralises approximately 100 USP heparin units. The amount of protamine required decreases over time as heparin is metabolised. 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 30 minutes after intravenous injection.

Administration of protamine sulphate 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 Sulphate Injection, USP products should be consulted.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

<table>
<thead>
<tr>
<th>Pharmacotherapeutic groups:</th>
<th>Blood and blood forming organs, Antithrombotic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC codes:</td>
<td>B01AB001</td>
</tr>
</tbody>
</table>

*Mechanism of action*
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 conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilising factor.

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.

Heparin does not have fibrinolytic activity; therefore it will not lyse existing clots. Clinical trials have not demonstrated the superiority of heparin in the maintenance of catheter patency over fluid not containing anticoagulant medication (eg. normal saline).
5.2 Pharmacokinetic properties
None presented.

5.3 Preclinical safety data
Carcinogenicity
No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin.

Mutagenesis
No reproduction studies in animals have been performed concerning mutagenesis.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Inactive ingredients: sodium chloride, citric acid monohydrate, sodium phosphate-dibasic dodecahydrate (Na₂HPO₄ 12H₂O), and water for injection.

6.2 Incompatibilities
Do not add other drugs to Heparin Sodium in 0.9% Sodium Chloride Intravenous Infusion.

6.3 Shelf life
24 months from date of manufacture.

6.4 Special precautions for storage
Store at or below 30°C.

6.5 Nature and contents of container
HEPARIN SODIUM is supplied in single dose VIAFLEX plastic bag containers for intravenous administration. HEPARIN SODIUM is available in the following presentations:

<table>
<thead>
<tr>
<th>Code No.</th>
<th>Name of the composition expressed in concentrations (g, mmol/Unit Vol)</th>
<th>Osmolarity (mOsmol/L)</th>
<th>ARTG/AUST R TT50-</th>
<th>Pack size (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHB0944</td>
<td>HEPARIN SODIUM, 2 IU/mL in Viaflex IV Bag - 1000mL</td>
<td>378 (350)§</td>
<td>19435, TT50-3874</td>
<td>1000 (12’s)</td>
</tr>
<tr>
<td></td>
<td><strong>Active:</strong> Heparin sodium (2000IU)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|            | **Excipients:**  
|            | Sodium chloride (9, 154);  
|            | Citric acid 1.H₂O (0.4, 1.9);  
|            | Sodium phosphate-dibasic 12.H₂O (5.8, 16.2) and  
|            | Water for injection to 1000mL                                         |                       |                   |                |
HEPARIN SODIUM Data Sheet 16 August 2018
Baxter Healthcare Ltd

<table>
<thead>
<tr>
<th>AHB0953</th>
<th>HEPARIN SODIUM, 2 IU/mL in Viaflex IV Bag - 500mL</th>
<th>378 (350)</th>
<th>19434, TT50-3874</th>
<th>500 (18's)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active:</strong></td>
<td>Heparin sodium (1000IU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Excipients:</strong></td>
<td>Sodium chloride (4.5, 77); Citric acid 1.H2O (0.2, 0.95); Sodium phosphate-dibasic 12.H2O (2.9, 8.1) and Water for injection to 500mL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

§Note: the osmolarity is a calculated figure, whilst the figures in brackets are approximate molality (mOsmol/kg).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicine or waste material should be disposed of in accordance with local requirements.

*Directions for use of Viaflex plastic container*

**WARNING** Do not use plastic containers in series connections. Such use could result in air-embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

*To Open*
Tear over pouch down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilisation process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found discard solution as sterility may be impaired.

**Do not add supplementary medication.**

*Preparation for administration*
Suspend container from eyelet support.

Remove plastic protector from outlet port at bottom of container.

Attach administration set. Refer to complete directions accompanying set.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
*HEPARIN SODIUM* is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.
HEPARIN SODIUM is distributed in Australia by:
Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
13 March 1986.

10 DATE OF REVISION OF THE TEXT
16 August 2018.

SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Document reformatted to SPC style.</td>
</tr>
</tbody>
</table>

Based on Australian PI approved on 20 December 2013 and RSI 2012 0821.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

Baxter and Viaflex are trademarks of Baxter International Inc.