PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

HEPARIN SODIUM and 0.9% SODIUM CHLORIDE INJECTION

Heparin Sodium for injection

1000 USP Heparin Units in 500mL 0.9% Sodium Chloride Injection

2000 USP Heparin Units in 1000mL 0.9% Sodium Chloride Injection

Intravenous solution

Anticoagulant

Baxter Corporation

7125 Mississauga Road,
Mississauga,
Ontario Canada L5N 0C2

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RECENT MAJOR LABEL CHANGES

2 Contraindications	03/2022
4 Dosage and Administration, 4.4 Administration	08/2022
7 Warnings and Precautions	03/2022
7 Warnings and Precautions, 7.1.1 Pregnant Women	03/2022
7 Warnings and Precautions, 7.1.2 Breast-feeding	03/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

HEPARIN SODIUM in 0.9% SODIUM CHLORIDE INJECTION is indicated for anticoagulant therapy:

- in extracorporeal circulation,
- in dialysis procedures,
- as an aid in the maintenance of catheter patency.

1.1 Pediatrics (< 12 years of age):

Safety and effectiveness in pediatric patients have not been established.

1.2 Geriatrics (> 60 years of age):

A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Clinical studies indicate that lower doses of heparin may be indicated in these patients (see 10 CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

Heparin sodium is contraindicated in patients:

- with uncontrollable bleeding (see 7 WARNINGS AND PRECAUTIONS), except when this is due to disseminated intravascular coagulation.
- with a known hypersensitivity to heparin sodium or porcine derivatives or to any ingredient in the formulation or component of the container (for a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- with a history of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis (HITT).
- with severe thrombocytopenia.
- when suitable blood coagulation tests cannot be performed at appropriate intervals (for full-dose heparin sodium therapy). There is usually no need to monitor the effect of low-dose heparin in patients with normal coagulation parameters.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Heparin Sodium is not effective by oral administration and Heparin Sodium and 0.9% Sodium Chloride Injection should not be given orally.

4.2 Recommended Dose and Dosage Adjustment

- Heparin administration procedures vary and are adjusted to the requirements of the individual patient by the attending physician, but a proper heparinization schedule MUST BE initiated before and maintained throughout dialysis to prevent clotting and subsequent blood path obstruction.
- Dosage is dependent upon the age, weight and clinical conditions of the patient, in addition to the procedure being employed.

4.4 Administration

Priming fluid should contain 2000 USP heparin units per 1000 mL of 0.9% Sodium Chloride Injection.

Visually inspect the container. If the administration port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless solution is clear and seal is intact. Use of a final filter is recommended during administration of all parenteral solutions, where possible.

Because dosages of this drug are titrated to response, **no additives should be made to Heparin Sodium and 0.9% Sodium Chloride Injection**.

It is recommended that the intravenous administration apparatus be replaced at least every 24 hours.

All injections in VIAFLEX Plus plastic containers are intended for administration using sterile equipment. Note: Read dialyzer direction sheets and follow manufacturer's directions for use.

DIRECTION FOR USE OF VIAFLEX PLUS 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.

Pressurizing intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

To Open

Tear overwrap downside at slit and remove solution container. Do not remove unit from overwrap until ready for use. The overwrap is a moisture barrier. The inner bag maintains the

sterility of the product. After removing overwrap, 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

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

5 OVERDOSAGE

Symptoms

Bleeding is the primary sign of heparin sodium 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.

If reversal of heparinization is desired or in the case of overdosage, protamine sulfate (1% solution) by slow infusion is utilized. **No more than 50 mg** should be given **very slowly** in a 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 units of heparin sodium (or 1.0 to 1.5 mg neutralizes approximately 1.0 mg of heparin). Heparins derived from various animal sources require different amounts of protamine sulfate for neutralization. This fact is of most importance during procedures of regional heparinization, including dialysis.

Decreasing amounts of protamine are required as time from the last heparin injection increases. For example, thirty minutes after a dose of heparin, approximately 0.5 mg of protamine is sufficient to neutralize each 100 USP units of heparin. Ideally, the dose required to neutralise the action of heparin should be guided by blood coagulation tests or calculated from a protamine neutralisation test.

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 labeling of protamine sulfate products should be consulted.

Blood or plasma transfusions may be necessary; these dilute but do not neutralize heparin.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Heparin Sodium and 0.9% Sodium Chloride Injection is a sterile nonpyrogenic solution of Heparin Sodium, USP derived from porcine intestinal mucosa, standardized for use as an anticoagulant, in 0.9% Sodium Chloride (NaCl) Injection.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution, 500 mL 1000 USP Heparin Units in 0.9% Sodium Chloride	• Citric Acid, USP • Dibasic Sodium Phosphate • Sodium Chloride • Water for Injection
Intravenous	Solution, 1000 mL 2000 USP Heparin Units in 0.9% Sodium Chloride	• Citric Acid, USP • Dibasic Sodium Phosphate • Sodium Chloride • Water for Injection

Osmolarity (actual): 358 mOsmol/L.

The pH of the solution is approximately 7.0.

The approximate ionic concentrations are as follows:

Approx. mmol/L	Sodium	186.4
	Chloride	154
	Phosphate (as HPO_4^{2-})	16.2
	Citrate	1.9
Approx. mEq/L	Sodium	186.4
	Chloride	154
	Phosphate (as HPO_4^{2-})	32.4
	Citrate	1.9

The VIAFLEX PLUS plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 plastic). Water can permeate from inside the container into the overwrap in amounts insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexylphthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

Heparin Sodium in 0.9% Sodium Chloride Injection is supplied in VIAFLEX PLUS plastic (polyvinyl chloride) containers.

7 WARNINGS AND PRECAUTIONS

General

Heparin is not intended for intramuscular use.

Do not use Heparin Sodium in 0.9% Sodium Chloride Injection as a "catheter lock flush" product. Heparin Sodium in 0.9% Sodium Chloride Injection is not suitable for this use. Use only products approved for catheter lock to perform catheter lock flush procedures.

Carefully examine all presentations of heparin sodium to confirm the correct formulation prior to administration of the drug.

Larger doses of heparin may be necessary in the febrile state.

Reactions which may occur because of the solution or the technique of administration of Heparin Sodium in 0.9% Sodium Chloride Injection include: febrile response; infection at the site of injection; venous thrombosis or phlebitis extending from the site of injection; extravasation; and hypervolemia.

Allergic reactions

Because Heparin Sodium is derived from animal tissue, it should be used with caution in patients with a history of allergy.

There is experimental evidence that heparin may modify or inhibit allergic reactions. However, the application of these findings to human patients has not been fully defined.

Hypersensitivity reactions have been reported with chills, fever and urticaria as the most usual manifestations. Asthma, rhinitis, lacrimation, and anaphylactoid reactions have also been reported.

Vasospastic reactions may develop independent of the origin of heparin, 6 to 10 days after the initiation of the therapy and last for 4 to 6 hours. The affected limb is painful, ischemic and cyanosed. An artery to this limb may have been recently catheterized. After repeat injections, the reaction may gradually increase to include generalized vasospasm, with cyanosis, tachypnea, feeling of oppression and headache.

Coagulation testing

Administration of Heparin Sodium when used in therapeutic dosage should be regulated by frequent blood coagulation tests. If the coagulation tests are unduly prolonged or if hemorrhage occurs, Heparin Sodium should be promptly discontinued (see 5 OVERDOSAGE).

Fluid balance

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

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 edema with sodium retention. Solutions containing sodium should be used with caution in patients receiving corticosteroids or corticotrophin.

Excessive administration of potassium free solutions may result in significant hypokalemia.

Hemorrhage

Avoid using heparin in the presence of major bleeding, except when the benefits of heparin therapy outweigh the potential risks.

Hemorrhage can occur at virtually any site in patients receiving heparin. Fatal hemorrhages have occurred. A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special populations, 7.1.4 Geriatrics). An unexplained fall in blood pressure, anemia and fall in hematocrit, or any other unexplained symptom should lead to serious consideration of hemorrhagic event (see 8 ADVERSE REACTIONS, 8.5 Post-market adverse reactions)). Hematocrit testing and tests for occult blood in stools should be performed periodically during heparin administration.

Heparin sodium should be used with extreme care in patients suffering from conditions in which there is increased danger of hemorrhage, for example:

Cardiovascular

Subacute bacterial endocarditis, arteriosclerosis, severe hypertension

Surgical

During and immediately following (a) spinal tap or spinal anaesthesia or (b) major surgery, especially involving the brain, spinal chord or eye.

Hematologic

Conditions associated with increased bleeding tendencies such as hemophilia, some

purpuras and thrombocytopenia.

Gastrointestinal

Conditions associated with inaccessible ulcerative lesions and continuous tube drainage of stomach or small intestine. Gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion.

Patients with hereditary antithrombin III deficiency receiving concurrent antithrombin III therapy (see 9 DRUG INTERACTIONS, 9.4 Drug-drug interactions)

Hepatic

Liver disease with impaired hemostasis.

Other: Menstruation and in patients with indwelling catheters.

Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:

- Adrenal hemorrhage with resultant acute adrenal insufficiency has occurred during anticoagulant therapy. Therefore, discontinue treatment in patients who develop signs and symptoms compatible with acute adrenal hemorrhage and insufficiency. Plasma cortisol levels should be measured immediately, and vigorous therapy with intravenous corticosteroids should be instituted promptly. Initiation of therapy should not depend upon laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.
- Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short or long-term anticoagulant therapy. This complication if unrecognized may be fatal.
- Retroperitoneal hemorrhage

Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis)

HIT is a serious immune-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as HIT with thrombosis (HITT). Thrombotic events may also be the initial presentation for HIT. 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 fatal outcomes.

Once HIT (with or without thrombosis) is diagnosed or strongly suspected, discontinue all heparin sodium sources (including heparin flushes) and use an alternative anticoagulant.

Immune-mediated HIT is diagnosed based on clinical findings supplemented by laboratory tests confirming the presence of antibodies to heparin sodium, or platelet activation induced by heparin sodium. Obtain platelet counts at baseline and periodically during heparin

administration. 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 sodium–naïve 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 all patients with HIT.

Monitor any degree of thrombocytopenia closely. If the platelet count falls below 100,000/mm3 or if recurrent thrombosis develops, promptly discontinue the heparin product, evaluate for HIT and HITT, and consider alternative anticoagulants if patients require continued anticoagulation.

HIT or HITT can occur up to several weeks after the discontinuation of heparin therapy. Evaluate patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin sodium for HIT or HITT.

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of up to 30%. It can occur 2 to 20 days (average 5 to 9) following the onset of heparin therapy. Platelet counts should be obtained at baseline and periodically during heparin administration. Mild thrombocytopenia (count greater than 100,000/mm3) 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/mm3 or if recurrent thrombosis develops (see **Heparin-induced Thrombocytopenia (HIT) With or Without Thrombosis**), promptly discontinue the heparin product, evaluate for HIT and HITT and, if necessary, administer an alternative anticoagulant.

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 anti-thrombin deficiency. Monitor coagulation tests closely in such patients. It may be necessary to adjust the dose of heparin based on anti-Factor Xa levels.

Hypersensitivity

Hypersensitivity reactions with chills, fever and urticaria as the most usual manifestations and also asthma, rhinitis, lacrimation, and anaphylactoid reactions have been reported. Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. Because Heparin Sodium in Sodium Chloride Injection is derived from animal tissue, it should be used with caution in patients with a history of allergy to pork products.

Hyperkalemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly in patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium, or taking potassium sparing drugs. The risk of hyperkalemia appears to increase with duration of therapy but is usually reversible upon discontinuation of heparin.

Measure plasma potassium in patients at risk of hyperkalemia before starting heparin therapy and periodically in all patients treated for more than 5 days or earlier as deemed fit by the clinician.

Investigations

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. Elevation of these enzymes in patients receiving heparin should be interpreted with caution.

Monitoring and Laboratory Tests

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance and electrolyte concentration and acid base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such an evaluation.

Periodic platelet counts, hematocrits, coagulation testing and tests for occult blood in stool are recommended during the entire course of heparin therapy.

Renal and Hepatic Impairment

Heparin sodium should be used with caution in patients with hepatic or renal disease.

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

7.1 Special Populations

7.1.1 Pregnant Women:

There are no adequate data from the use of Heparin in pregnant women.

Animal reproduction studies have not been conducted with Heparin Sodium and 0.9% Sodium Chloride Injection. It is also not known whether Heparin Sodium and 0.9% Sodium Chloride Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin Sodium and 0.9% Sodium Chloride Injection should be given to a pregnant woman only if clearly needed and if the potential benefit justifies the potential risk to the fetus. Heparin sodium does not cross the placental barrier.

7.1.2 Breast-feeding:

Nursing Women: Due to its large molecular weight, Heparin Sodium is not likely to be excreted in human milk.

There are no adequate data from the use of Heparin in lactating women. Physicians should carefully consider the potential risks and benefits for each patient before prescribing Heparin to breast-feeding women.

7.1.3 Pediatrics (< 12 years of age):

Safety and effectiveness in pediatric patients have not been established.

7.1.4 Geriatrics (> 60 years of age):

A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Clinical studies indicate that lower doses of heparin may be indicated in these patients (see 10 CLINICAL PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic counter-measures, and save the remainder of the fluid for examination if deemed necessary.

8.2 Clinical Trial Adverse Reactions

There are no data available on adverse reactions from Baxter-controlled clinical trials conducted with heparin sodium.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience and/or are known to have been reported with the use of heparin sodium. These reactions are listed by MedDRA System Organ Class (SOC), then by preferred term in order of severity.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Heparin-induced thrombocytopenia (HIT), Heparin-induced thrombocytopenia and thrombosis (HITT), Heparin-associated thrombocytopenia (HAT), Delayed HITT, Acute reversible thrombocytopenia (see 7 WARNINGS AND PRECAUTIONS).

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction and shock, Anaphylactoid reaction and Hypersensitivity.

ENDOCRINE DISORDERS: Adrenal hemorrhage (with resultant acute adrenal insufficiency), Suppression of aldosterone synthesis.

METABOLISM AND NUTRITION DISORDERS: Rebound hyperlipemia (upon withdrawal of heparin), Hyperkalaemia.

NERVOUS SYSTEM DISORDERS: Headache.

VASCULAR DISORDERS: Venous thrombosis or Phlebitis, Extravasation, Haemorrhage, Epistaxis, Contusion, Vasospastic reactions (including episodes of painful, ischemic, and cyanosed limbs).

GASTROINTESTINAL DISORDERS: Retroperitoneal hemorrhage, Gastrointestinal hemorrhage, Nausea and Vomiting.

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Asthma, Rhinitis, Cyanosis, Tachypnea.

EYE DISORDERS: Lacrimation.

SKIN AND SUBCUTANEOUS TISSUE DISORDER: Erythema, Skin necrosis, Urticaria, Delayed Transient Alopecia, Itching and Burning, especially on the plantar side of the feet.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Osteoporosis, Arthralgia.

RENAL AND URINARY DISORDERS: Suppression of renal functions, Haematuria.

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Ovarian cyst (corpus luteum haemorrhage), Priapism.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Chest pain, Febrile response, Injection site reactions, Chills and Fever, Sense of oppression, Local irritation, Mild pain, Hematoma or Ulceration.

INJURY, POISONING, AND PROCEDURAL COMPLICATIONS: Post procedural hematoma.

INVESTIGATIONS: Elevated blood pressure, Elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

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 NSAIDS (e.g., acetylsalicylic acid, phenylbutazone, ibuprofen, indomethacin, and celecoxib), dextran, epoprostenol, clopidogrel, thienopyridines, dipyridamole, hydroxychloroquine, glycoprotein IIb/IIIa antagonists (including abciximab, eptifibatide, and tirofiban), and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients), may induce bleeding and should be used with caution in patients receiving heparin.

Antithrombin III (human)

The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. To reduce the risk of bleeding, reduce the heparin dose during concomitant treatment with antithrombin III (human).

Other Interactions

Digitalis, tetracyclines, nicotine or antihistamines may partially counteract the anticoagulant action of heparin sodium.

Intravenous nitroglycerin administered to patients receiving heparin 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.

The use of ACE inhibitors and angiotensin-II antagonists in conjunction with heparin increase the risk of hyperkalemia.

When administering Heparin concomitantly with the drugs listed above monitor coagulation tests frequently and adjust Heparin dose as necessary.

9.7 Drug-Laboratory Test Interactions

Hyperaminotransferasemia

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. Elevations that might be caused by drugs (like heparin) should be interpreted with caution.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Heparin sodium inhibits reactions which lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. Heparin sodium acts at multiple sites in the normal coagulation system. Small amounts of heparin sodium in combination with antithrombin III (heparin co-factor) can prevent the development of a hypercoagulable state by inactivating activated Factor X, preventing the conversion of prothrombin to thrombin. Once a hypercoagulable state exists, larger amounts of heparin sodium in combination with antithrombin III can inhibit the coagulation process by inactivating thrombin and earlier clotting intermediates, thus preventing the conversion of fibrinogen to fibrin. Heparin sodium also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin sodium. Clotting time is prolonged by full therapeutic doses of heparin sodium; in most cases it is not measurably affected by low doses of heparin sodium. Heparin sodium does not have fibrinolytic activity; therefore it will not lyse existing clots.

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.

10.3 Pharmacokinetics

Peak plasma levels of heparin sodium are achieved 2 to 4 hours following subcutaneous administration, although there are considerable individual variations. Loglinear plots of heparin sodium plasma concentrations with time, for a wide range of dose levels, are linear, which suggests the absence of zero order processes. The liver and the reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10 min.), 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 sodium.

The plasma half-life is approximately 1½ hours, however the half-life increases with increasing doses ranging from approximately 1 hour with a dose of 100 units/kg to approximately 2½ hours with a dose of 400 units/kg.

Special Populations and Conditions

The plasma half-life may be prolonged in patients with cirrhosis or severe renal impairment. Patients with pulmonary embolism may have a more rapid clearance of heparin sodium. Heparin sodium is not removed by hemodialysis.

11 STORAGE, STABILITY AND DISPOSAL

Protect from freezing.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. It is recommended the product be stored at room temperature (15-25°C); brief exposure up to 40°C does not adversely affect the product.

12 SPECIAL HANDLING INSTRUCTIONS

See 11 STORAGE, STABILITY AND DISPOSAL.

Heparin Sodium in 0.9% Sodium Chloride Injection should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use of a final filter is recommended during administration of all parenteral solutions, where possible. Do not administer unless the solution is clear and colorless, and the seal is intact.

For single use only. Discard any unused portion.

Do not reconnect partially used bags.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

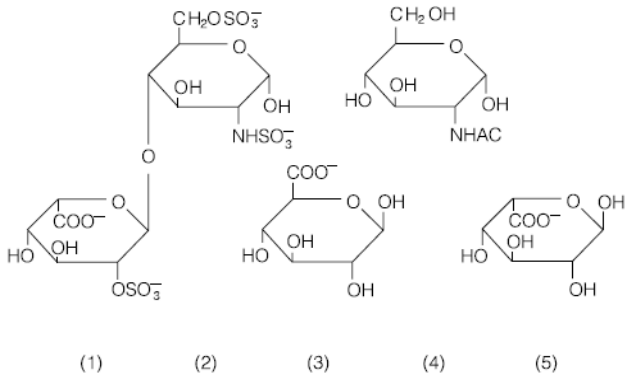
Drug Substance – Heparin Sodium

Proper name: Heparin sodium, USP

Chemical name: Heparin sodium

Molecular formula and molecular mass: NaCl, 58.54g/mol

Structural formula:



Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, having anticoagulant properties. 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) ß-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. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions.

Physicochemical properties: Soluble in water, glycerol. Very slightly soluble in alcohol.

Product Characteristics:

Heparin Sodium and 0.9% Sodium Chloride Injection is a sterile nonpyrogenic solution of Heparin Sodium, USP derived from porcine intestinal mucosa, standardized for use as an anticoagulant. The anticoagulant potency of the heparin sodium is determined by a biological assay using a USP reference.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Studies on the carcinogenic potential, reproductive and developmental toxicity, and genotoxic potential of the components of Heparin Sodium and 0.9% Sodium Chloride Injection have not been performed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION

Heparin Sodium, USP and Sodium Chloride, USP

Read this carefully before you start taking Heparin Sodium in 0.9% Sodium Chloride Injection and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Heparin Sodium in 0.9% Sodium Chloride Injection**.**

What is Heparin Sodium in 0.9% Sodium Chloride Injection used for?

This medication belongs to a group of medicines known as anticoagulants. Heparin Sodium in 0.9% Sodium Chloride Injection is used as anticoagulant in extracorporeal circulation and dialysis procedure. It is also used as an aid in maintenance of catheter patency.

How does Heparin Sodium in 0.9% Sodium Chloride Injection work?

This medication works by decreasing the clotting ability of your blood and helps to stop clots from forming in the blood vessels.

What are the ingredients in Heparin Sodium in 0.9% Sodium Chloride Injection?

Medicinal ingredients: Heparin Sodium, USP

Sodium Chloride, USP

Non-medicinal ingredients: Citric Acid, Anhydrous, USP

Dibasic Sodium Phosphate, USP

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

Heparin Sodium in 0.9% Sodium Chloride Injection comes in the following dosage forms:

- Intravenous solution of 1000 USP Heparin Units in 500mL 0.9% Sodium Chloride Injection
- Intravenous solution of 2000 USP Heparin Units in 1000mL 0.9% Sodium Chloride Injection

Do not use Heparin Sodium in 0.9% Sodium Chloride Injection if:

Do not use this medication if you have had or currently have any of the following:
• A known allergy to heparin, pork, or sulfites.
• a severe decrease in the number of platelets in the blood
• uncontrollable bleeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Heparin Sodium in 0.9% Sodium Chloride Injection. Talk about any health conditions or problems you may have, including if you:

- you are having an epidural or spinal anaesthetic. It is important that you remind your doctor that you are receiving heparin infusion before you receive any anaesthetic
- you have or have had in the past, injury or surgery on the brain, spinal cord, or eyes
- you have any condition which makes you likely to bleed more easily, regardless of the reason. Ask your doctor if unsure.
- you are menstruating.
- you often consume alcohol.
- you suffer from kidney or liver problems.
- you are pregnant or nursing or may become pregnant.
- you are over 60 years of age.
- you have a severe decrease in the number of platelets in the blood
- you have bacterial infection inside of the heart (bacterial endocarditis)
- you have high blood pressure (hypertension)
- you have ulcerative lesions of the small intestine or stomach

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Heparin Sodium in 0.9% Sodium Chloride Injection

- Drugs that affect blood clotting (e.g. anticoagulants, antithrombotic drugs, platelet inhibitors, and thrombolytics). You may be likely to bleed more easily.
- Non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for arthritis or pain. You may be likely to bleed more easily
- Salicylates (such as aspirin) for reducing pain and inflammation, or for stopping harmful blood clots from forming. You may be likely to bleed more easily
- Digitalis, tetracyclines, nicotine, and antihistamines. These medications may partially counteract the anticoagulant activity of heparin sodium

How to take Heparin Sodium in 0.9% Sodium Chloride Injection

Usual dose:

Your doctor will determine your dosage according to the results of suitable laboratory tests. The rate for infusion of the medication is dependent upon age, weight, clinical condition of the patient and the procedure being employed.

Administration:
Heparin is not intended for intramuscular use.
Your doctor should not use Heparin Sodium in 0.9% Sodium Chloride Injection for catheter lock flush procedure.

Overdose:

Bleeding is the primary sign of heparin sodium overdosage. Nosebleeds, blood in urine, tarry stools or easy bruising may be noted as the first sign of bleeding.

If you think you, or a person you are caring for, have taken too much Heparin Sodium in 0.9% Sodium Chloride Injection contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Heparin Sodium in 0.9% Sodium Chloride Injection?

This medication may cause side effects. These are not all the possible side effects you may have when taking Heparin Sodium in 0.9% Sodium Chloride Injection. If you experience any side effects not listed here, tell your healthcare professional. Ask your doctor or nurse to answer any questions that you may have.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Frequency not known			
Tingling, weakness or numbness in legs or lower body, back pain, loss of control of bowel or bladder after epidural or spinal anaesthesia			√
Signs of stroke (bleeding in the brain) such as severe headache, severe nausea and vomiting, dizziness, confusion			√
Signs of bleeding in the abdomen: abdominal or stomach pain, back pain, blood in urine or stool, vomiting of blood, black stool (tarry stool)			√
Signs of allergic reaction to medication: rash, itching, hives on the skin, swelling of the face,			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
lips, tongue or other parts of the body, shortness of breath, wheezing, trouble breathing			
Chest pain, rapid or unusual heartbeat			√
Bleeding episodes, unexplained nosebleeds, heavy menstrual periods, bleeding from gums while brushing teeth, bleeding or oozing from surgical wounds			√
Spontaneous bruising (bruise not caused by injury)			√
Unexplained skin lesions (sores)			√
Pain or swelling of legs or feet			√
Discoloration (purple or red) and pain around the injection site		√	
Prolonged, painful erection			√
Fever		√	
Chills		√	

The above events were reported in the post-marketing setting.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15 to 25°C). Protect from freezing. Excessive heat should be avoided.

Keep out of reach and sight of children.

If you want more information about Heparin Sodium in 0.9% Sodium Chloride Injection

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.baxter.ca or by contacting the sponsor, Baxter Corporation, at: 1-800-387-8399. .

This leaflet was prepared by Baxter Corporation,

Mississauga, ON L5N 0C2.

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