PRODUCT MONOGRAPH

HEPARIN SODIUM INJECTION USP

For intravenous or subcutaneous use

10 000 USP units per mL

Anticoagulant

Pfizer Canada ULC
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Kirkland, Quebec
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
IV infusion, intermittent IV injection, or deep SC injection	Solution 10 000 units/mL	Preservative: Benzyl Alcohol (9.45 mg/ml)

INDICATIONS AND CLINICAL USE

Heparin Sodium Injection is indicated for:

- prophylaxis and treatment of venous thrombosis and its extension
- prophylaxis and treatment of pulmonary embolism
- prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation
- prevention of clotting in arterial and heart surgery
- prophylaxis and treatment of peripheral arterial embolism
- anticoagulant use in blood transfusions, extracorporeal circulation and dialysis procedures
- diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation)

Geriatrics (> 60 years of age):
There are limited adequate and well-controlled studies in patients 65 years and older. However a higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Lower doses of heparin may be indicated in these patients (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics (<16 years):
There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

Heparin Sodium Injection should not be used in patients:

- with severe thrombocytopenia or a history of heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis or a history of thrombocytopenia with pentosan polysulfate.
- with a known hypersensitivity to heparin or pork products or to any ingredient in the formulation (eg. anaphylactoid reactions). For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- in whom, suitable blood coagulation tests (e.g., the whole blood clotting time, partial thromboplastin time) cannot be performed at appropriate intervals. This contraindication refers to full-dose heparin regimens only; there is usually no need to monitor coagulation parameters in patients receiving low-dose heparin.
- with an uncontrollable active bleeding state (see WARNINGS AND PRECAUTIONS), except when this is due to disseminated intravascular coagulation.

Heparin Sodium Injection should not be used in neonates, premature and low birth weight infants because the formulation contains benzyl alcohol (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Do not use Heparin Sodium Injection as a "catheter lock flush" product. Heparin Sodium Injection is supplied in vials containing various strengths of heparin. Including vials that contain a highly concentrated solution of 10 000 units in 1 mL. Fatal hemorrhages have occurred in pediatric patients due to medication errors in which 1 mL Heparin Sodium Injection vials were confused with 1 mL "catheter lock flush" vials. Carefully examine all Heparin Sodium Injection vials to confirm the correct vial choice prior to administration of the drug.

General

Heparin is not intended for intramuscular use.

Use only if solution is clear and container and seals are intact.

Hemorrhage

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

Hemorrhage can occur at virtually any site in patients receiving heparin. Fatal hemorrhages have occurred. Adrenal hemorrhage (with resultant acute adrenal insufficiency), ovarian hemorrhage and retroperitoneal hemorrhage have occurred during anticoagulant therapy with heparin. A higher incidence of bleeding has been reported in patients over 60 years of age, particularly in women.

An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a hemorrhagic event.

Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage, including:

- Cardiovascular: Subacute bacterial endocarditis. Severe hypertension.

- Surgical: During and immediately following (a) spinal tap, spinal or epidural anesthesia or (b) major surgery, especially involving the brain, spinal cord or eye.

- Hematologic: Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia and some vascular purpuras.

- Gastrointestinal: Ulcerative lesions and continuous tube drainage of the stomach or small intestine, and clinical settings in which stress-induced gastrointestinal hemorrhage is possible.

- Patients with hereditary antithrombin III deficiency receiving concurrent antithrombin III therapy: 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: Menstruation, liver disease with impaired hemostasis, severe renal disease, or in patients with indwelling catheters.

Hematologic

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 known as Heparin-induced Thrombocytopenia and Thrombosis (HITT). 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. Monitor thrombocytopenia of any degree closely. If the platelet count falls below 100,000/mm^3 or if recurrent thrombosis develops, promptly discontinue heparin, evaluate for HIT and HITT, and, if necessary, administer an alternative anticoagulant.

HIT and 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.

Thrombocytopenia: Thrombocytopenia in patients receiving heparin has been reported with frequencies up to 30% and may appear from 4-21 days after the start of treatment, although it may occur sooner if there is a history of heparin-induced thrombocytopenia. 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, associated with positive or unknown in vitro platelet antibody test results in the presence of heparin or if recurrent thrombosis develops, promptly discontinue heparin product, evaluate for HIT and HITT and, if necessary, administer an alternative anticoagulant.

Epidural or Spinal Anesthesia: In patients undergoing epidural or spinal anesthesia, or lumbar puncture, the prophylactic use of heparin has been associated with epidural or spinal hematomas, which may result in prolonged or permanent paralysis. The risk is increased by the use of epidural or spinal catheters for anesthesia, by concomitant use of drugs affecting coagulation such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors and by traumatic or repeated punctures.

Hyperkalemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly 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 usually reversible with discontinuation of heparin.

Heparin resistance

Resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, in postsurgical patients, and patients with antithrombin III deficiency. Close monitoring of coagulation tests is recommended in these cases. Adjustment of heparin doses based on anti-Factor Xa levels may be warranted.

Heparin Hypersensitivity

Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations.

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

Benzyl Alcohol Toxicity

The preservative benzyl alcohol has been associated with serious adverse events including the "gasping syndrome" and death in pediatric patients. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low birth weight infants may be more likely to develop toxicity. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Concomitant use of Heparin with Andexanet Alfa

Unresponsiveness to unfractionated heparin leading to non-prolongation of activated clotting times and serious thrombotic events has occurred when unfractionated heparin was administered after use of andexanet alfa for the reversal of direct Factor Xa inhibitors (apixaban and rivaroxaban). Avoid use of heparin after use of andexanet alfa. Use an alternative anticoagulant to heparin.

Carcinogenesis and Mutagenesis

No long term studies in animals have been performed with Heparin Sodium Injection to evaluate the carcinogenic potential of heparin. No studies in animals have been performed addressing mutagenesis or impairment of fertility.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies on heparin use in pregnant women.

Although heparin sodium does not cross the placenta based on human and animal studies, heparin sodium should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus. If used during pregnancy, it should be administered with caution especially during the last trimester and withdrawn one or two days before the delivery date, due to the risk of fetal-maternal hemorrhage.

Heparin use during pregnancy has been associated with adverse events including perinatal death and prematurity.

Long-term usage of therapeutic doses of heparin during pregnancy may increase the risk of osteoporosis and vertebral fractures.

Heparin Sodium Injection includes benzyl alcohol as a preservative. There are no known adverse outcomes associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration, however products containing benzyl alcohol should be given to pregnant patients with caution as the benzyl alcohol molecule, given its small size, presumably crosses the placental barrier into immature fetal tissues as readily as it crosses the blood-brain barrier.

In a published study conducted in rats and rabbits, pregnant animals received heparin intravenously during organogenesis at a dose of 10 000 units/kg/day, approximately 10 times the maximum daily dose based on body weight. The number of early resorptions increased in both species. There was no evidence of teratogenic effects.

Nursing Women:
Due to its large molecular weight, heparin is not likely to be excreted in human milk, and any heparin in milk would not be orally absorbed by a nursing infant. Heparin Sodium Injection contains benzyl alcohol as a preservative. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. Exercise caution when administering Heparin Sodium Injection to a nursing mother.

Neonates, premature and low birth weight infants:
Carefully examine all heparin drug product containers to confirm choice of the correct strength prior to administration of the drug. Pediatric patients, including neonates, have died as a result of medication errors in which Heparin Sodium Injection vials have been confused with “catheter lock flush” vials (see WARNINGS AND PRECAUTIONS). Do not use Heparin Sodium Injection in neonates, premature and low birth weight infants because the formulation contains benzyl alcohol.

Pediatrics (<16 years of age):
There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience (see DOSAGE AND ADMINISTRATION).

Fatal Medication Errors: Heparin is supplied in a wide range of strengths. Fatal hemorrhages have occurred in infants and pediatric patients due to medication errors in which 1 mL Heparin Sodium Injection vials were confused with 1 mL “catheter lock flush” vials. Carefully examine all heparin products to ensure that the proper strength is selected for administration (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions).

The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome" and death in children younger than 3 years of age (see WARNINGS AND PRECAUTIONS, Benzyl Alcohol Toxicity).

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 ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

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 hemorrhage occurs, discontinue heparin promptly (see OVERDOSAGE).

Periodic platelet counts, hematocrits, and tests for occult blood in the stool are recommended during the entire course of heparin therapy, regardless of the route of administration (see DOSAGE AND ADMINISTRATION).

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

Precautions for I.V. administration

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

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

These solutions are intended for intravenous administration using sterile equipment. It is recommended that any unused heparin solution and intravenous administration apparatus be replaced at least once every 24 hours.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

1. Hemorrhage.

Hemorrhage is the chief complication that may result from heparin therapy (see WARNINGS AND PRECAUTIONS). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see OVERDOOSAGE). **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 hemorrhagic complications may be difficult to detect:

a. Adrenal hemorrage, 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 hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.
b. 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.
c. Retroperitoneal hemorrhage
d. Spinal hematoma and epidural hematoma

2. Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT), Heparin-induced Thrombocytopenia and Thrombosis (HITT) and delayed Onset of HIT and HITT. (see WARNINGS AND PRECAUTIONS.)

3. Local Irritation.
Local irritation, erythema, mild pain, hematoma 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.

4. Hypersensitivity.
Generalized 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 less frequently. Itching and burning, especially on the plantar site of the feet, may occur. (see WARNINGS AND PRECAUTIONS.)

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of up to 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 possibly death. (see WARNINGS AND PRECAUTIONS).

Certain episodes of painful, ischemic 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.

5. Bone and Joint
   Therapeutic doses of heparin administered for longer than 3months have been associated with osteoporosis and spontaneous vertebral fractures. Osteoporosis may be reversible after discontinuation of heparin.

6. Osteoporosis following long-term administration of high doses of heparin.

7. Miscellaneous
   Cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapsim, and rebound hyperlipemia on discontinuation of heparin sodium have also been reported.

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

   Hyperkalemia has also been reported.

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of the injection, extravasation, and hypervolemia.

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reaction data from clinical trials are not available.

Post Market Adverse Drug Reactions:

Adverse reaction rates associated with the use of heparin sodium in clinical practice have been reviewed[1]. Incidence rates in the following table are taken from this review.

Table 1. Adverse reaction rates reported in the literature

Adverse Reaction	Incidence
Hemorrhage	Major bleeding: up to 7% Fatal bleeding: up to 2%
Thrombocytopenia Heparin Induced Thrombocytopenia (HIT) Heparin Induced Thrombocytopenia and Thrombosis (HITT) Delayed Onset HIT and HITT	HIT rate1-3%
Miscellaneous - osteoporosis	Osteopenia rate up to one-third of patients on long term therapy (osteopenia may lead to osteoporosis)

[1] Niccolai CS, Hicks RW, Oertel L, Francis JL: Heparin Consensus Group. Unfractionated heparin: focus on a high-alert drug. Pharmacotherapy. 2004 Aug; 24 (8Pt2):146S-155S

DRUG INTERACTIONS

Overview

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

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

Concomitant use of thrombolytic agents such as alteplase, streptokinase may also increase the risk of hemorrhage.

Concomitant use of some contrast media may also affect the coagulation process and increase the risk of hemorrhage.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2. Summary of drug-drug Interactions with heparin

Drug	Interaction
Drugs Enhancing Heparin Effect: Drugs interfering with platelet aggregation: - Systemic salicylates, - NSAIDs, including celecoxib and ibuprofen - Glycoprotein IIb/IIIa antagonists - Thienopyridines - Dipyridamole - Hydroxychloroquine - Dextran - Antithrombin III (human)	May induce bleeding, Prolongation of one-stage prothrombin time (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 to obtain a valid prothrombin time). Enhances anticoagulant effect of heparin in patients with hereditary antithrombin III deficiency. (To reduce the risk of bleeding, a reduced dose of heparin is recommended during treatment with antithrombin III (human)
Drugs Decreasing Heparin Effect: - Digitalis - Tetracycline - Nicotine - Nitrates - Antihistamines - Andexanet alfa	May partially counteract the anticoagulant action of heparin sodium. (Monitor patients' coagulation tests appropriately) May reduce the effectiveness of heparin. (Andexanet alfa, a recombinant modified human coagulation factor Xa used for reversal of anticoagulation with apixaban or rivaroxaban, has been shown to bind to heparin-bound antithrombin III (ATIII) and may reduce the anticoagulant effect of heparin. See **Warnings and Precautions**.)

Effect of Heparin on Other drugs

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

Drug-Food Interactions
Heavy alcohol drinkers are at greater risk of major heparin associated bleeding than moderate or non-drinkers.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Table 3. Important Drug-Laboratory Interactions

Drug / Laboratory Interaction	Significance	Notes
Significant elevations of aminotransferase AST (SGOT) or Significant elevations of aminotransferase ALT (SGPT)	Aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.	Hyperaminotransferasemia: Significant elevations of aminotransferase levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.
Prothrombin time	Heparin sodium may prolong the one-stage prothrombin time	When heparin sodium is given with warfarin, allow a period of at least 5 hours after the last intravenous or 24 hours after the last subcutaneous dose of heparin to elapse before blood is drawn to obtain a valid prothrombin time.

DOSAGE AND ADMINISTRATION

Dosing Considerations
The product should be administered under the supervision of a qualified health professional who is experienced in the use of anticoagulant agents and in the management of patients with venous thrombosis, pulmonary embolism, acute and chronic consumptive coagulopathies and peripheral arterial embolism. Appropriate management of therapy and complications is only possible when adequate diagnostic treatment facilities are readily available.

Preparation for Administration

Confirm the choice of the correct Heparin Sodium Injection vial to ensure that the 1 mL vial is not confused with a "catheter lock flush" vial or other 1 mL vial of incorrect strength (see WARNINGS AND PRECAUTIONS).

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use only if solution is clear and the seal is intact. Do not use if solution is discoloured or contains precipitate.

When Heparin Sodium Injection is added to an infusion solution for continuous intravenous (IV) administration, invert the container at least six times to ensure adequate mixing and prevent pooling of the heparin in the solution. Storage of prepared infusion solution should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C. Heparin Sodium Solution is incompatible with certain substances in solution (eg., alteplase, amikacin sulphate, atracurium besylate, ciprofloxacin, cytarabine, daunorubicin, droperidol, erythromycin lactobionate, gentamicin sulfate, idarubicin, kakamycin sulfate, mitoxantrone HCl, polymyxin B sulfate, promethazine HCl, streptomycin sulfate, tobramycin sulfate).

Administer Heparin Sodium Injection by intermittent IV injection, IV infusion or deep subcutaneous (intrafat, i.e. above the iliac crest or abdominal fat layer) injection. Heparin Sodium Injection is not intended for intramuscular (IM) use (see ADVERSE REACTIONS, Local Irritation).

Laboratory Monitoring for Efficacy and Safety

Adjust the dosage of Heparin Sodium Injection 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. When initiating treatment with Heparin Sodium Injection by continuous intravenous infusion, determine the coagulation status (aPTT, INR, platelet count) at baseline and continue to follow aPTT approximately every 4 hours and at appropriate intervals thereafter. When the drug is administered intermittently by intravenous injection, perform coagulation tests before each injection during initiation of treatment and at appropriate intervals thereafter. After deep subcutaneous (SC) injections, tests for adequacy of dosage are best performed on samples drawn 4 to 6 hours after the injections.

Periodic platelet counts and hematocrits are recommended during the entire course of Heparin Sodium Injection therapy, regardless of the route of administration.

Therapeutic Anticoagulant Effect with Full-Dose Heparin

The dosing recommendations in Table 4 are based on clinical experience. Although dosages must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage schedules may be used as guidelines:

Table 4.
Recommended Adult Full-Dose Heparin Regimens for Therapeutic Anticoagulant Effect

METHOD OF ADMINISTRATION	FREQUENCY	RECOMMENDED DOSE*
Deep Subcutaneous (Intrafat) Injection Use a different site for each injection to prevent the development of hematoma	Initial Dose	333 units/kg subcutaneously
	Every 12 hours	250 units/kg subcutaneously
Intermittent Intravenous Injection	Initial Dose	10 000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, USP
	Every 4 to 6 hours	5 000 to 10 000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection , USP
Continuous Intravenous Infusion	Initial Dose	5 000 units by IV injection
	Continuous	20 000 to 40 000 units per 24 hours in 1000 mL of 0.9% Sodium Chloride Injection, USP or Dextrose 5% for infusion

* Based on 150 lb (68 kg) patient

Pediatric Use
Do not use Heparin Sodium Injection in neonates, premature and low birth weight infants. The preservative benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants.

There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience. In general, the following dosage schedule may be used as a guideline in pediatric patients:

Initial Dose: 75 to 100 units/kg (IV bolus over 10 minutes)

Maintenance Dose:
Infants: 25 to 30 units/kg/hour;
Infants < 2 months have the highest requirements (average 28 units/kg/hours
Children > 1 year of age: 18 to 20 units/kg/hour;
Older children may require less heparin, similar to weight-adjusted adult dosage

Monitoring:	Adjust heparin to maintain aPTT of 60 to 85 seconds, assuming this reflects an anti-Factor Xa level of 0.35 to 0.70

Geriatric Use
Patients over 60 years of age may require lower doses of heparin. (see WARNINGS AND PRECAUTIONS.)

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

Low-Dose Prophylaxis of Postoperative Thromboembolism
The most widely used dosage has been 5,000 units 2 hours before surgery and 5,000 units every 8 to 12 hours thereafter for 7 days or until the patient is fully ambulatory, whichever is longer. Administer the heparin by deep subcutaneous (intrafat, i.e. above the iliac crest or abdominal fat layer) injection with a fine (25 to 26-guage) needle to minimize tissue trauma.

Blood Transfusion
Addition of 400 to 600 units per 100 mL of whole blood is usually employed to prevent coagulation. Usually, 7,500 USP units of heparin sodium are added to 100 mL of 0.9% Sodium Chloride Injection, USP (or 75,000 USP units per 1,000 mL of 0.9% Sodium Chloride Injection, USP) and mixed; from this sterile solution, 6 to 8 mL are added per 100 mL of whole blood.

Converting to Warfarin
To ensure continuous anticoagulation when converting from Heparin Sodium Injection to warfarin, continue full heparin therapy for several days until the INR (prothrombin time) has reached a stable therapeutic range. Heparin therapy may then be discontinued without tapering (see DRUG INTERACTIONS).

Converting to Dabigatran
For patients currently receiving intravenous heparin, stop intravenous infusion of heparin sodium immediately after administering the first dose of oral dabigatran (PRADAXA®); or for intermittent intravenous administration of heparin sodium, start oral dabigatran 0 to 2 hours before the time that the next dose of heparin was to have been administered.

Extracorporeal Dialysis
Follow equipment manufacturers' operating directions carefully. A dose of 25 to 30 units/kg followed by an infusion rate of 1,500 to 2,000 units/hour is suggested based on pharmacodynamic data if specific manufacturers' recommendations are not available.

Missed Dose:
The product should only be administered under the supervision of a qualified health professional who is experienced in the use of anticoagulant agents, and missed doses are not to be expected.

OVERDOSAGE

For management of a suspected drug overdosage, contact your regional Poison Control Centre.

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 heparinization, protamine sulfate (1% solution) by slow infusion will neutralize heparin sodium. **No more than 50 mg** should be administered **very slowly**, in any 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 USP Heparin Units. The amount of protamine required decreases over time as heparin is metabolized. 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 ½ hour after intravenous injection.

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

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

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Heparin inhibits reactions that lead to the clotting of blood and formation of fibrin clots both *in vitro* and *in vivo.* Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of Factor XIII, the fibrin stabilizing factor. Heparin does not have fibrinolytic activity.

Pharmacodynamics

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.

Pharmacokinetics

Absorption	Peak plasma levels of heparin are achieved 2-4 hours following subcutaneous administration, although there are considerable individual variations. Log-linear plots of heparin plasma concentrations with time for a wide range of dose levels are linear which suggests the absence of zero order processes.
Distribution	The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.
Metabolism	Liver and the reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10 minutes) and after the age of 40, a slower beta phase, indicates uptake in the organs.
Excretion	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. 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. Heparin is not removed by hemodialysis.

Special Populations and Conditions

Geriatrics: 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.

STORAGE AND STABILITY

Exposure of products to heat should be minimized. Avoid excessive heat. Protect from freezing.

Invert container and carefully inspect the solution in good light for cloudiness, haze or particulate matter. Any container which is suspect should not be used.

It is recommended that the product be stored in the commercial vials at room temperature (20º-25ºC).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Heparin Sodium Injection is supplied in clear Type 1 vials with a bromobutyl rubber stoppers and color coded overseals for each strength to reduce the potential for dosing errors.
Heparin Sodium Injection USP is available as:

- 10 000 units per mL: with preservative, 10 000 unit in 2 mL vials (1 mL fill) Available in packs of 25 vials (multiple doses)

Nonmedicinal ingredients:

10 000 units/mL vials contain sodium hydroxide and hydrochloric acid (to adjust pH), Water for Injection and benzyl alcohol as preservative (9.45 mg/ml).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

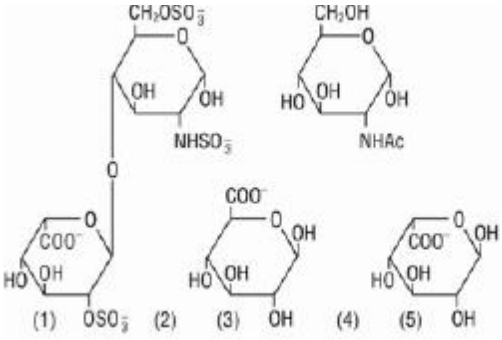
Drug Substance

Proper name: Heparin sodium

Chemical name: Heparin sodium

Molecular formula and molecular mass:
Heparin is a heterogeneous group of straight-chain anionic mucopolysaccarides, called glycosaminoglycans having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) alpha-L-iduronic acid-2-sulfate, (2) 2-deoxy-2-sulfamino-alpha-D-glucose 6-sulfate, (3) beta-D-glucuronic acid, (4) 2-acetamido-2-deoxy-alpha-D-glucose, and (5) alpha-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glucosidic 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.

Molecular structure of heparin sodium (representative units):



Physicochemical properties: Crude Heparin is derived from North American sourced porcine intestinal tissue.

Description: White or almost white powder

Solubility: Freely soluble in water

pH: 5.5 to 8.0 for a 1% aqueous solution

CLINICAL TRIALS

The clinical effectiveness of Heparin, in the mentioned indications, has been determined through many years of clinical use and is described in a number of published studies and clinical practice guidelines.

REFERENCES

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6. Ibarra-Perez C, Lau-Cortes E, Colmenero-Zubiate S, Arevila-CeballosN, Fong JH, Sanchez-Martinez R, Dominguez MV, Elizalde- Gonzalez J. Prevalence and prevention of deep venous thrombosis of the lower extremities in high-risk pulmonary patients. Angiology 1988, 39:505-513.

7. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. Lancet 1997, 349:1569-1581.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Heparin Sodium Injection USP

This leaflet is Part III of a three-part "Product Monograph" published when Heparin Sodium Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Heparin Sodium Injection. Contact your doctor or pharmacist if you have any questions about this drug.

ABOUT THIS MEDICATION

What the medication is used for

Heparin Sodium Injection is indicated for:

- treatment to stop your blood from clotting in many surgical and non-surgical situations
- preventing and stopping the spread of blood clots in your veins
- preventing and stopping the spread of blood clots to your lungs
- treatment of some disorders of blood clotting
- prevention of blood clotting during surgery
- prevention and treatment of blood clots in your arteries

What it does

Heparin stops reactions that lead to the clotting of blood and the formation of clots. Once an active blood clot has developed, larger amounts of heparin can inhibit further clotting.

Peak levels of heparin are achieved 2-4 hours following intravenous administration, although there are considerable individual variations.

When it should not be used

BEFORE you use Heparin Sodium Injection, talk to your doctor if you have:

- severe reduction of blood platelets
- an uncontrollable active bleeding state (see **WARNINGS AND PRECAUTIONS)**, except when this is due to disseminated intravascular coagulation
- a hypersensitivity or allergy to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **What the important nonmedicinal ingredients are.**

This Heparin Sodium Injection formulation contains benzyl alcohol and should not be given to neonates, premature and low birth weight infants.

What the medicinal ingredient is
Heparin sodium

What the important nonmedicinal ingredients are
Sodium chloride
Benzyl alcohol as preservative

What dosage form it comes in
Heparin Sodium Injection is available as:
- 10 000 units per mL: vials of 10 000 units in 2 mL (1 mL fill) with preservative

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Fatal bleeding has occurred in infants and children due to medication errors in which 1 mL Heparin Sodium Injection vials were confused with 1 mL "catheter lock flush' vials.

Bleeding can occur at virtually any site in patients receiving heparin.

Increased resistance to heparin is frequently encountered in fever, blood clot, vein inflammation associated with a blood clot, infection with blood clotting tendencies, heart attack, cancer and in patients after surgery.

Heparin sodium should be used with extreme caution in disease states in which there is an increased danger of bleeding. Some of the conditions in which an increased danger of bleeding exists are:
- Infections of the heart and heart valves. Severe high blood pressure.
- During and immediately following (a) spinal tap, spinal or epidural anesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.
- Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia (low platelets) and some vascular purpuras.
- Ulcers of the stomach and continuous tube drainage of the stomach or small intestine.
- Menstruation, liver disease with impaired blood clotting.

Heparin sodium should be used with caution in patients at risk of increased potassium levels.

Excessive administration of potassium-free solutions may result in significant low concentrations of potassium in the blood.

Heparin is not intended for Intramuscular Use.

Allergic reaction to this drug might happen, stop the medication and consult your doctor.

Platelet count should be tested and monitored.

This Heparin Sodium Injection formulation contains benzyl alcohol and should be given with caution to pregnant and nursing women.

INTERACTIONS WITH THIS MEDICATION

Certain medications may intensify the anticoagulant effect (e.g., blood thinning effect) of Heparin Sodium Injection. Therefore, it is important for you to advise your doctor if you are taking any medications such as the following:

- other drugs used to reduce blood clotting including warfarin, dextran, alteplase or streptokinase
- acetylsalicylic acid (Aspirin)
- non-steroidal anti-inflammatory drugs (NSAIDs); drugs used to treat painful and/or inflammatory conditions of muscles or joints including ibuprofen, celecoxib or indomethacin
- hydroxychloroquine; drug used to treat malaria
- Andexanet alpha can cause unresponsiveness to Heparin Sodium.

The following may interact with ONDEXXYA:
• ONDEXXYA treatment should be avoided if anticoagulation with heparin might become necessary.
ONDEXXYA causes unresponsiveness to heparin.

PROPER USE OF THIS MEDICATION

If you think you, or a person you are caring for, have taken too much Heparin Sodium Injection USP, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

Usual dose

The product should be administered under the supervision of a qualified health professional who is experienced in the use of anticoagulant agents and in the management of patients with venous thrombosis, pulmonary embolism, acute and chronic consumptive coagulopathies and peripheral arterial embolism. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- irritation at the injection site
- mild pain at the injection site

- bruising at the injection site
- chills
- fever
- skin rash
- asthma
- runny nose
- tearing from eyes
- headache
- nausea
- vomiting

If the above symptoms become bothersome consult your doctor.

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	
COMMON Hemorrhage; bleeding			√
Thrombocytopenia; low levels of platelets in the blood			√
Osteoporosis after prolonged treatment		√	
RARE Allergic reactions			√

This is not a complete list of side effects. For any unexpected effects while taking Heparin Sodium Injection, contact your doctor or pharmacist immediately.

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

MORE INFORMATION

- 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 www.pfizer.ca or by calling 1-800-463-6001.

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