

Hemorrhage - Hemorrhage is the chief complication that may result from heparin therapy *[see Warnings and Precautions (5.1)]*. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug *[see Overdosage (10)]*. 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:

- Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy, including fatal cases.
- Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short- or long-term anticoagulant therapy.
- Retroperitoneal hemorrhage.

HIT and HITT, including delayed onset *[see Warnings and Precautions (5.2)]*

Histamine-like reactions: Such reactions have been observed at the site of injections. Necrosis of the skin has been reported at the site of subcutaneous injection of heparin, occasionally requiring skin grafting.

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 more rarely. Itching and burning, especially on the plantar site of the feet, may occur *[see Warnings and Precautions (5.5)]*.

Elevations of serum aminotransferases - Significant elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have occurred in patients who have received heparin.

Others - 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 hyperlipemia on discontinuation of heparin sodium have also been reported.

7 DRUG INTERACTIONS

7.1 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.

7.2 Platelet Inhibitors

Drugs such as NSAIDs (including acetylsalicylic acid, ibuprofen, indomethacin, and celecoxib), dextran, phenylbutazone, thienopyridines, dipyridamole, hydroxychloroquine, glycoprotein IIb/IIa 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 sodium. To reduce the risk of bleeding, a reduction in the dose of the antiplatelet agent or heparin is recommended.

7.3 Other Medications that May Interfere with Heparin

Digitalis, tetracyclines, nicotine or antihistamines may partially counteract the anticoagulant action of heparin sodium. Intravenous nitroglycerin administered to heparinized patients may result in a decrease of the partial thromboplastin time with subsequent rebound effect upon discontinuation of nitroglycerin. Careful monitoring of partial thromboplastin time and adjustment of heparin dosage are recommended during coadministration of heparin and intravenous nitroglycerin.

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, a reduced dosage of heparin is recommended during treatment with antithrombin III (human).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Heparin Sodium in Sodium Chloride Injection use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In published reports, heparin exposure during pregnancy did not show evidence of an increased risk of adverse maternal or fetal outcomes in humans *(see Data)*. Consider the benefits and risks of HEPARIN SODIUM IN SODIUM CHLORIDE INJECTION for the mother and possible risks to the fetus when prescribing HEPARIN SODIUM IN SODIUM CHLORIDE INJECTION.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

The maternal and fetal outcomes associated with uses of heparin via various dosing methods and administration routes during pregnancy have been investigated in numerous studies. These studies generally reported normal deliveries with no maternal or fetal bleeding and no other complications.

Animal Data

In a published study conducted in rats and rabbits, pregnant animals received heparin intravenously during organogenesis at a dose of 10,000 USP units/kg/day, approximately >50 times the human daily dose. The number of early resorptions increased in both species. There was no evidence of teratogenic effects.

8.2 Lactation

Risk Summary

There is no information regarding the presence of heparin in human milk, the effects on the breastfed child, or the effects on milk production. Due to its large molecular weight, heparin is not likely to be excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for HEPARIN SODIUM IN SODIUM CHLORIDE INJECTION and any potential adverse effects on the breastfed child from HEPARIN SODIUM IN SODIUM CHLORIDE INJECTION or from the underlying maternal condition *[see Use in Specific Populations (8.4)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

A higher incidence of bleeding has been reported in patients over 60 years of age, especially women *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

Bleeding is the chief sign of heparin overdosage.

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 1/2 hour after intravenous injection.

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

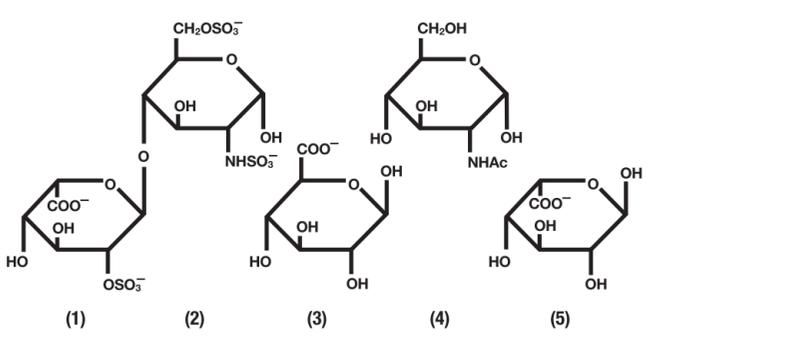
For additional information, consult the prescribing information for Protamine Sulfate Injection, USP.

11 DESCRIPTION

Intravenous solutions with heparin sodium (derived from porcine intestinal mucosa) are sterile, nonpyrogenic fluids for intravenous administration. Each 100 mL contains heparin sodium 200 USP Units; sodium chloride, 0.9 g; citric acid, anhydrous, 37 mg and dibasic sodium phosphate, heptahydrate, 430 mg added as buffers. Each liter contains the following electrolytes: Sodium 186.1 mEq; phosphate (as HPO₄⁼) 32.1 mEq; citrate 5.8 mEq; and chloride 153.9 mEq. Osmolar concentration, 358 mOsmol/liter (calc.); pH 7.0 (5.0 – 7.5).

Heparin Sodium, USP 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) 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) > (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. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

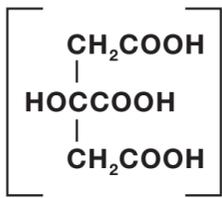
Structure of Heparin Sodium (representative subunits):



Sodium Chloride, USP is chemically designated NaCl, a white crystalline compound freely soluble in water.

Dibasic Sodium Phosphate, USP (Heptahydrate), is chemically designated (Na₂HPO₄ 7H₂O), colorless or white granular salt freely soluble in water.

Citric Acid, USP, anhydrous is chemically designated C₆H₈O₇, colorless, translucent crystals or white crystalline powder very soluble in water. It has the following structural formula:



Water for Injection, USP is chemically designated H₂O.

The **freeflex**® container closure system is not made from natural rubber latex, is Non-PVC and Non-DEHP. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Heparin interacts with the naturally occurring plasma protein, Antithrombin III, to induce a conformational change, which markedly enhances the serine protease activity of Antithrombin II, thereby inhibiting the activated coagulation factors involved in the closing sequence, particularly Xa and IIa. Small amounts of heparin inhibit Factor Xa, and larger amounts inhibit thrombin (Factor IIa).

Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor. Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

12.2 Pharmacodynamics

Various times (activated clotting time, activated partial thromboplastin time, prothrombin time, whole blood clotting time) are prolonged by full therapeutic doses of heparin; in most cases, they are not measurably affected by low doses of heparin. Bleeding time is usually unaffected by heparin.

12.3 Pharmacokinetics

Absorption

Heparin is not absorbed through the gastrointestinal tract and therefore administered via parenteral route. Peak plasma concentration and the onset of action are achieved immediately after intravenous administration.

Distribution

Heparin is highly bound to antithrombin, fibrinogens, globulins, serum proteases and lipoproteins. The volume of distribution is 0.07 L/kg.

Elimination

Metabolism

Heparin does not undergo enzymatic degradation.

Excretion

Heparin is mainly cleared from the circulation by liver and reticuloendothelial cells mediated uptake into extravascular space. Heparin undergoes biphasic clearance, a) rapid saturable clearance (zero order process due to binding to proteins, endothelial cells and macrophage) and b) slower first order elimination. The plasma half-life is dose-dependent and it ranges from 0.5 to 2 h.

Specific Populations

Geriatric Patients

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 *[see Use in Specific Populations (8.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term studies in animals have been performed to evaluate carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

13.2 Fertility Studies

16 HOW SUPPLIED/STORAGE AND HANDLING

Intravenous solutions with heparin sodium are available in single-dose containers as follows:

Product Code	Unit of Sale	Strength	Unit of Use
519077	NDC 63323-519-77 Unit of 24	Heparin Sodium 1,000 USP Units per 500 mL (2 USP Units per mL) in 0.9% Sodium Chloride	NDC 63323-519-02 500 mL freeflex ® bag
519100	NDC 63323-519-10 Unit of 12	Heparin Sodium 2,000 USP Units per 1,000 mL (2 USP Units per mL) in 0.9% Sodium Chloride	NDC 63323-519-01 1,000 mL freeflex ® bag

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing.

16.1 Storage and Handling

17 PATIENT COUNSELING INFORMATION

Hemorrhage

Inform patients that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they are treated with heparin, and that they should report any unusual bleeding or bruising to their physician. Hemorrhage can occur at virtually any site in patients receiving heparin. Fatal hemorrhages have occurred *[see Warnings and Precautions (5.1)]*.

Prior to Surgery

Advise patients to inform physicians and dentists that they are receiving heparin before any surgery is scheduled *[see Warnings and Precautions (5.1)]*.

Heparin-Induced Thrombocytopenia

Inform patients of the risk of heparin-induced thrombocytopenia (HIT). HIT may progress to the development of venous and arterial thromboses, a condition known as heparin-induced thrombocytopenia and thrombosis (HITT). HIT can occur up to several weeks after the discontinuation of heparin therapy *[see Warnings and Precautions (5.2)]*.

Hypersensitivity

Inform patients that generalized hypersensitivity reactions have been reported. Necrosis of the skin has been reported at the site of subcutaneous injection of heparin *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

Other Medications

Because of the risk of hemorrhage, advise patients to inform their physicians and dentists of all medications they are taking, including non-prescription medications, and before starting any new medication *[see Drug Interactions (7)]*.

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	FRESENIUS KABI
Lake Zurich, IL 60047	
Made in Norway	
www.fresenius-kabi.com/us	
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