HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION safely and effectively. See full prescribing information for HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION.

HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION, for intravenous use
Initial U.S. Approval: 1992

---------- INDICATIONS AND USAGE ----------

HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION at the concentration of 2 USP units/mL is an anticoagulant indicated for:
- Maintenance of catheter patency (1)

---------- DOSAGE AND ADMINISTRATION ----------

Although the rate of infusion of the 2 USP units/mL formulation is dependent upon the age, weight, clinical condition of the patient, and the procedure being employed, an infusion rate of 3 mL/hour has been found to be satisfactory. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Heparin Sodium 1,000 USP units per 500 mL (2 USP units per mL) in 0.9% Sodium Chloride Injection (3)

---------- CONTRAINDICATIONS ----------

- History of Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) (4)
- Known hypersensitivity to heparin or pork products (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Fatal Medication Errors: Confirm choice of correct strength prior to administration. (5.1)
- Hemorrhage: Fatal cases have occurred. Use caution in conditions with increased risk of hemorrhage. (5.2)
- HIT (With or Without Thrombosis): Monitor for signs and symptoms and discontinue if indicative of HIT (With or Without Thrombosis). (5.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are: hemorrhage, thrombocytopenia, HIT (with or without thrombosis), hypersensitivity reactions, and elevations of aminotransferase levels. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact B. Braun Medical Inc. at 1-800-227-2862 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

- Drugs that interfere with platelet aggregation may induce bleeding. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Heparin Sodium Injection in 0.9% Sodium Chloride at the concentration of 2 USP units/mL is indicated as an anticoagulant to maintain catheter patency.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Confirm the selection of the correct formulation and strength prior to administration of the drug.

This product should be administered by intravenous infusion.

Do not use Heparin Sodium in 0.9% Sodium Chloride Injection as a “catheter lock flush” product.

Do not admix with other drugs.

Do not use plastic containers in series connection.

This product should not be infused under pressure.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.2 Maintenance of Catheter Patency

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

3 DOSAGE FORMS AND STRENGTHS

- Heparin Sodium 1,000 USP units per 500 mL (2 USP units per mL) in 0.9% Sodium Chloride Injection.

4 CONTRAINDICATIONS

The use of HEPARIN SODIUM is contraindicated in patients:

- With history of heparin-induced thrombocytopenia (HIT) (With or Without Thrombosis) [*see Warnings and Precautions (5.3)*]
- With a known hypersensitivity to heparin or pork products (e.g., anaphylactoid reactions) [*see Adverse Reactions (6.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Fatal Medication Errors

Do not use this product as a “catheter lock flush” product. Heparin is supplied in various strengths. Fatal hemorrhages have occurred due to medication errors. Carefully examine all heparin products to confirm the correct container choice prior to administration of the drug.

5.2 Hemorrhage

Hemorrhage, including fatal events, has occurred in patients receiving HEPARIN SODIUM. 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. Adrenal hemorrhage (with resultant acute adrenal insufficiency), ovarian hemorrhage, and retroperitoneal hemorrhage have occurred during anticoagulant therapy with heparin *[see Adverse Reactions (6.1)]*. A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age *[see Clinical Pharmacology (12.3)]*. An unexplained fall in hematocrit or fall in blood pressure should lead to serious consideration of a hemorrhagic event.

Use heparin sodium with caution in disease states in which there is increased risk of hemorrhage, including:

- Cardiovascular — Subacute bacterial endocarditis. Severe hypertension.
- Surgical — During and immediately following (a) spinal tap or spinal 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.
- 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).
- Gastrointestinal — Ulcerative lesions and continuous tube drainage of the stomach or small intestine. **Other** — Menstruation, liver disease with impaired hemostasis.

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

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 HIT with thrombosis. 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, thrombus formation on a prosthetic cardiac valve, 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, if necessary, administer an alternative anticoagulant.

HIT 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.

5.4 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. Obtain platelet counts before and periodically during heparin therapy. Monitor thrombocytopenia of any degree closely. If the count falls below 100,000/mm^3 or if recurrent thrombosis develops, promptly discontinue heparin, evaluate for HIT, and, if necessary, administer an alternative anticoagulant *[see Warnings and Precautions (5.3)]*.

5.5 Hypersensitivity Reactions

Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. *[see Adverse Reactions (6.1)]*.

Because Heparin Sodium in 0.9% Sodium Chloride Injection is derived from animal tissue, monitor for signs and symptoms of hypersensitivity when it is used in patients with a history of allergy.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Fatal Medication Errors *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.2)]*
- Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) *[see Warnings and Precautions (5.3)]*
- Thrombocytopenia *[see Warnings and Precautions (5.4)]*
- Hypersensitivity [*see Warnings and Precautions (5.5)*]

6.1 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of heparin sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

- **Hemorrhage -** Hemorrhage is the chief complication that may result from heparin therapy [*see Warnings and Precautions (5.2)*]. 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 with heparin 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.
- **Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) and Thrombocytopenia**: [*see Warnings and Precautions (5.3 and 5.4)*]

- **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 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 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In published reports, heparin exposure during pregnancy did not show evidence of an increased risk of adverse maternal or fetal outcomes in humans. No teratogenicity was observed in animal reproduction studies with administration of heparin sodium to pregnant rats and rabbits during organogenesis at doses, approximately 2777 times the recommended human dose (MRHD) for maintenance of catheter patency of heparin [*see Data*]. In pregnant animals, doses up to 2777 times higher than the human daily dose of heparin resulted in increased resorptions. Consider the benefits and risks of HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION to a pregnant woman and possible risks to the fetus when prescribing HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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 2777 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 SODIUM IN 0.9% SODIUM CHLORIDE INJECTION in human milk, the effects on the breastfed infant, or the effects on milk production. 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. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION and any potential adverse effects on the breastfed infant from HEPARIN SODIUM IN 0.9% SODIUM CHLORIDE INJECTION or from the underlying maternal condition [*see Use in Specific Populations (8.4)*].

8.4 Pediatric Use

There are no adequate and well controlled studies on heparin use in pediatric patients.

8.5 Geriatric Use

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 [*see Warnings and Precautions (5.2)*].

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.

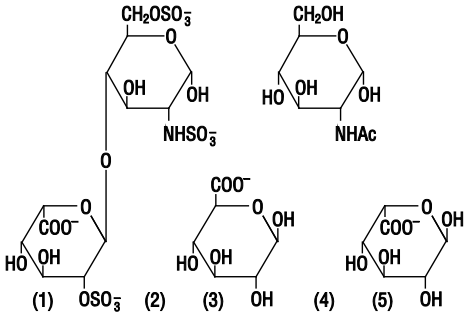
Because fatal reactions often resembling anaphylaxis have been reported, protamine sulfate should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

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

11 DESCRIPTION

Heparin is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans having anticoagulant properties. It is composed of polymers of alternating derivations of alpha-L-iduronic acid 2-sulfate (1), 2-deoxy-2-sulfamino-alpha-D-glucose 6-sulfate (2), beta-D-glucuronic acid (3), 2-acetamido-2-deoxy-alpha-D-glucose (4), and alpha-L-iduronic acid (5).

Structure of Heparin Sodium (representative subunits):



Heparin Sodium 1,000 USP units per 500 mL (2 USP units per mL) in 0.9% Sodium Chloride Injection is a sterile, nonpyrogenic solution prepared from Heparin Sodium USP (derived from porcine intestinal mucosa and standardized for use as an anticoagulant) in 0.9% Sodium Chloride Injection. It is to be administered by intravenous injection. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

Each 100 mL contains 0.43 g Dibasic Sodium Phosphate•7H_2O USP and 0.037 g Citric Acid Anhydrous USP as a buffer system, 0.9 g Sodium Chloride USP, and Water for Injection USP qs.

pH: 7.0 (6.8-7.2); Calculated Osmolarity: 360 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 186; Chloride 154; Phosphate ($HPO_4^{=}$) 32; Citrate 6

The plastic container is made from a multilayered film specifically developed for parenteral drugs. It contains no plasticizers and exhibits virtually no leachables. The solution contact layer is a rubberized copolymer of ethylene and propylene. The container is nontoxic and biologically inert. The container-solution unit is a closed system and is not dependent upon entry of external air during administration. The container is overwrapped to provide protection from the physical environment and to provide an additional moisture barrier when necessary.

The plastic container is not made with natural rubber latex, PVC or DEHP.

The closure system has two ports; the one for the administration set has a tamper evident plastic protector.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

12.2 Pharmacodynamics

Bleeding time is usually unaffected by heparin.

12.3 Pharmacokinetics

Loglinear plots of heparin plasma concentrations with time for a wide range of dose levels are linear which suggests the absence of zero order processes. Liver and the reticuloendothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{½}$ = 10 minutes) 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to evaluate the carcinogenic potential, reproduction studies in animals to determine effects on fertility of males and females, and studies to determine mutagenic potential have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

Heparin Sodium in 0.9% Sodium Chloride Injection is supplied sterile and nonpyrogenic in Full Fill 500 mL EXCEL® Containers packaged 24 per case.

NDC	REF	Concentration	Size
0264-9872-10	P8721	Heparin Sodium 1,000 USP units per 500 mL (2 USP units per mL) in 0.9% Sodium Chloride Injection	500 mL

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

Storage in automated dispensing machines: Brief exposure up to 2 weeks to ultraviolet or fluorescent light does not adversely affect the product labeling legibility; prolonged exposure can cause fading of the red label. Rotate stock frequently.

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 (5.2)].*

Prior to Surgery

Advise patients to inform physicians and dentists that they are receiving heparin before any surgery is scheduled *[see Warnings and Precautions (5.2)]*.

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 (With or Without Thrombosis) can occur up to several weeks after the discontinuation of heparin therapy [*see Warnings and Precautions (5.3 and 5.4)*].

Hypersensitivity

Inform patients that generalized hypersensitivity reactions have been reported.

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 (7.1)]*.

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B. Braun Medical Inc.
Bethlehem, PA 18018-3524 USA
1-800-227-2862
Y36-002-901 LD-240-6