HEPARIN SODIUM AND DEXTROSE- heparin sodium injection, solution
Hospira, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HEPARIN SODIUM IN 5% DEXTROSE INJECTION safely and effectively. See full prescribing information for HEPARIN SODIUM IN 5% DEXTROSE INJECTION.

HEPARIN SODIUM IN 5% DEXTROSE INJECTION, for intravenous use
Initial U.S. Approval: 1939

INDICATIONS AND USAGE

HEPARIN SODIUM IN 5% DEXTROSE INJECTION is indicated for: (1)

- Prophylaxis and treatment of venous thrombosis and pulmonary embolism
- Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation
- Treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation)
- Prevention of clotting in arterial and cardiac surgery
- Prophylaxis and treatment of peripheral arterial embolism
- Anticoagulant use in blood transfusions, extracorporeal circulation and dialysis procedures

DOSAGE AND ADMINISTRATION

Recommended Adult Dosages:

- Therapeutic Anticoagulant Effect with Full-Dose Heparin* (2.3)

Intermittent Intravenous Injection	Initial Dose	10,000 Units, either undiluted or in 50 to 100 mL of 5% Dextrose Injection
	Every 4 to 6 hours	5,000 to 10,000 Units, either undiluted or in 50 to 100 mL of 5% Dextrose Injection
Continuous Intravenous Infusion	Initial Dose	5,000 Units by intravenous injection
	Continuous	20,000 to 40,000 Units/24 hours in 1000 mL of 5% Dextrose Injection

*Based on 150 lb. (68 kg) patient.

- Cardiovascular Surgery (2.5)

Intravascular via Total Body Perfusion	Initial Dose	≥150 units/kg; adjust for longer procedures

- Extracorporeal Dialysis (2.8)

Intravascular via Extracorporeal Dialysis	Follow equipment manufacturer's operating directions carefully.

For pediatric dosing see section 2.4 of full prescribing information.

DOSAGE FORMS AND STRENGTHS

- Heparin Sodium 25,000 USP units per 250 mL (100 USP units per mL) in 5% Dextrose Injection (3)
- Heparin Sodium 10,000 USP units per 100 mL (100 USP units per mL) in 5% Dextrose Injection (3)
- Heparin Sodium 12,500 USP units per 250 mL (50 USP units per mL) in 5% Dextrose Injection (3)

CONTRAINDICATIONS

- History of Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) (4)
- Known hypersensitivity to heparin or pork products (4)
- In whom suitable blood coagulation tests cannot be performed at appropriate intervals (4)
- With an uncontrollable active bleeding state, except when treating disseminated intravascular coagulation (4)
- Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn 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)
- Monitoring: Blood coagulation tests guide therapy for full-dose heparin. Monitor platelet count and hematocrit in all patients receiving heparin. (5.5)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

Drugs that interfere with coagulation, platelet aggregation or drugs that counteract coagulation may induce bleeding. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HEPARIN SODIUM IN 5% DEXTROSE INJECTION is indicated for:

- Prophylaxis and treatment of venous thrombosis and pulmonary embolism;
- Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation;
- Treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation);
- Prevention of clotting in arterial and cardiac surgery;
- Prophylaxis and treatment of peripheral arterial embolism;
- Anticoagulant use in blood transfusions, extracorporeal circulation and dialysis procedures.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

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

Do not use HEPARIN SODIUM IN 5% DEXTROSE 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.

Do not administer unless the solution is clear and container is undamaged.

Discard unused portion

To Open
Tear outer wrap at notch and remove solution container.

(Use aseptic technique)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. NOTE: See full directions on administration set carton.
4. Suspend container from hanger.

5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with flow control clamp.

Warning: Do not use flexible container in series connections.

2.2 Laboratory Monitoring for Efficacy and Safety

The dosage of heparin sodium should be adjusted according to the patient's coagulation test results. When heparin is given by continuous intravenous infusion, the coagulation time should be determined approximately every 4 hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each injection during the early stages of treatment and at appropriate intervals thereafter. 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.

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

2.3 Therapeutic Anticoagulant Effect with Full-Dose Heparin

The dosing recommendations in Table 1 are based on clinical experience. Although dosage 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 1: Recommended Adult Full-Dose Heparin Regimens for Therapeutic Anticoagulant Effect

Method of Administration	**Frequency**	**Recommended Dose***
Intermittent Intravenous Injection	Initial Dose	10,000 Units, either undiluted or in 50 to 100 mL of 5% Dextrose Injection
	Every 4 to 6 hours	5,000 to 10,000 Units, either undiluted or in 50 to 100 mL of 5% Dextrose Injection
Continuous Intravenous Infusion	Initial Dose	5,000 Units by intravenous injection
	Continuous	20,000 to 40,000 Units/24 hours in 1000 mL of 5% Dextrose Injection

* Based on 150 lb. (68 kg) patient.

2.4 Pediatric Use

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 (intravenous bolus over 10 minutes)

Maintenance Dose	Infants: 25 to 30 units/kg/hour; Infants < 2 months have the highest requirements (average 28 units/kg/hour) 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.

2.5 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.

2.6 Converting to Warfarin

To ensure continuous anticoagulation when converting from heparin sodium 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 (7.4)]*.

2.7 Converting to Oral Anticoagulants other than Warfarin

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

2.8 Extracorporeal Dialysis

Follow equipment manufacturer's 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.

3 DOSAGE FORMS AND STRENGTHS

HEPARIN SODIUM IN 5% DEXTROSE INJECTION is available as:

- Heparin Sodium 25,000 USP units per 250 mL (100 USP units per mL) in 5% Dextrose Injection.
- Heparin Sodium 10,000 USP units per 100 mL (100 USP units per mL) in 5% Dextrose Injection.
- Heparin Sodium 12,500 USP units per 250 mL (50 USP units per mL) in 5% Dextrose 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)]*
- In whom suitable blood coagulation tests — e.g., the whole blood clotting time, partial thromboplastin time, etc., — cannot be performed at appropriate intervals (this contraindication refers to full-dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low-dose heparin) *[see Warnings and Precautions (5.5)]*
- With an uncontrollable active bleeding state *[see Warnings and Precautions (5.5)]*, except when

treating disseminated intravascular coagulation.
- Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

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)]*. These patients may require a lower dose. 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 immune-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred 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 fatal outcomes.

Once HIT (with or without thrombosis) is diagnosed or strongly suspected, all heparin sodium sources (including heparin flushes) should be discontinued and an alternative anticoagulant used. Future use of heparin sodium, especially within 3 to 6 months following the diagnosis of HIT (with or without thrombosis), and while patients test positive for HIT antibodies, should be avoided.

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

Delayed Onset of HIT (With or Without Thrombosis): Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) 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 (With or Without Thrombosis).

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. 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 or if recurrent thrombosis develops, *[see Warnings and Precautions (5.3)]*, the heparin product should be discontinued, and, if necessary, an alternative anticoagulant administered.

5.5 Coagulation Testing and Monitoring

When heparin sodium is administered in therapeutic amounts, its dosage should be monitored by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if hemorrhage occurs, heparin sodium should be discontinued promptly *[see Overdosage (10)]*. Periodic platelet counts, hematocrits and tests for occult blood in stool are recommended during the entire course of heparin therapy *[see Dosage and Administration (2.2)]*.

5.6 Heparin Resistance

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

5.7 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 5% DEXTROSE INJECTION is derived from animal tissue, monitor for signs and symptoms of hypersensitivity when it is used in patients with a history of allergy.

This product contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

6 ADVERSE REACTIONS

The following clinically significant 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)]*
- Heparin Resistance *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*

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 or establish a causal relationship to drug exposure.

Hemorrhage

Hemorrhage is the chief complication that may result from heparin therapy *[see Warnings and Precautions (5.2)]*. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug *[see Overdose (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:

a. Adrenal hemorrhage, 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.

Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) and Delayed Onset of HIT (With or Without Thrombosis): *[see Warnings and Precautions (5.3, 5.4)]*

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.

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 (5.7)]*.

Episodes of painful, ischemic, and cyanosed limbs been reported with heparin use.

Elevations of serum aminotransferases

Significant elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have occurred in a high percentage of patients (and healthy subjects) 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.

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 injection, extravasation, and hypervolemia.

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 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.

7.3 Other Interactions

Digitalis, tetracyclines, nicotine, antihistamines, or intravenous nitroglycerine 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.

7.4 Drug/Laboratory Tests Interactions

Prothrombin time – Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with warfarin, allow a period of at least 5 hours after the last intravenous dose or 24 hours after the last subcutaneous dose of heparin to elapse before blood is drawn to obtain a valid prothrombin time.

Hyperaminotransferasemia

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. Since 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on HEPARIN SODIUM IN 5% DEXTROSE 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. No teratogenicity, but early embryo-fetal death was observed in animal reproduction studies with administration of heparin sodium to pregnant rats and rabbits during organogenesis at doses approximately 10 times the maximum recommended human dose (MRHD) of 40,000 USP units/24 hours infusion (*see Data*). Consider the benefits and risks of HEPARIN SODIUM IN 5% DEXTROSE INJECTION to a pregnant woman and possible risks to the fetus when prescribing HEPARIN SODIUM IN 5% DEXTROSE INJECTION.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a 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 10 times the maximum human daily dose based on body weight. 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 5% DEXTROSE INJECTION 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, and any heparin in milk would not be orally absorbed by a nursing child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HEPARIN SODIUM IN 5% DEXTROSE INJECTION and any potential adverse effects on the breastfed child from HEPARIN SODIUM IN 5% DEXTROSE 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. Pediatric dosing recommendations are based on clinical experience *[see Dosage and Administration (2.4)]*.

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)]*. Lower doses of heparin may be indicated in these patients *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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 1/2 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.

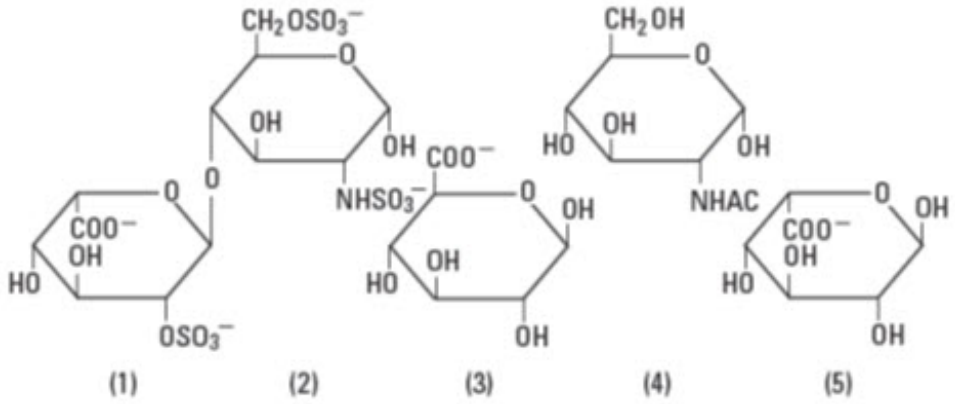
For additional information the labeling of Protamine Sulfate Injection, USP products should be consulted.

11 DESCRIPTION

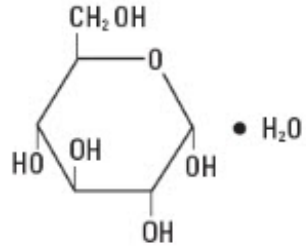
Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, called

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) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2)>(1)>(4)>(3)>(5), and are joined by glycosidic linkages, forming polymers of varying sizes. 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.

Structure of Heparin Sodium (representative subunits):



Dextrose, USP is chemically designated D-glucose, monohydrate C6H12O6 · H2O, a hexose sugar freely soluble in water. It has the following structural formula:



Water for Injection, USP is chemically designated H2O.

Intravenous solutions with heparin sodium (derived from porcine intestinal mucosa) are sterile, nonpyrogenic fluids for intravenous administration. Each 100 mL contains heparin sodium 4,000, 5,000 or 10,000 USP Units; dextrose, hydrous 5 g; citric acid, anhydrous, 51 mg and sodium citrate, dihydrate 334 mg added as buffers; sodium metabisulfite 20 mg added as an antioxidant. Each liter contains electrolytes sodium and citrate in amounts as listed in HOW SUPPLIED/STORAGE AND HANDLING Table. See Table for summary of contents and characteristics of this solution. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

The flexible plastic container is fabricated from a specially formulated nonplasticized, thermoplastic co-polyester (CR3). 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 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. Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

12.2 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.

12.3 Pharmacokinetics

Absorption

Heparin is not absorbed through 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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Intravenous solutions with heparin sodium are available in single-dose flexible plastic containers in various sizes and concentrations as shown in the accompanying Table as follows:

		Contents and Characteristics Per 100 mL							
Unit of Sale	**Product**	**Heparin Sodium (USP Units/mL)**	**Heparin Sodium (USP Units)**	**Dextrose (hydrous)**	**Sodium mEq/L**	**Citrate mEq/L**	**Tonicity**	**Solution Volume**	**Each**
NDC 0409-7793-62 Case of 24	Heparin Sodium 25,000 USP Units/250 mL (100 USP Units/mL) in 5% Dextrose Injection	100	10,000	5 g	39	42	Isotonic	250 mL	NDC 0409-7793-52
NDC 0409-7793-23 Case of 24	Heparin Sodium 10,000 USP Units/100 mL (100 USP Units/mL) in 5% Dextrose Injection	100	10,000	5 g	39	42	Isotonic	100 mL	NDC 0409-7793-13
NDC 0409-7794-62 Case of 24	Heparin Sodium 12,500 USP Units/250 mL (50 USP Units/mL) in 5% Dextrose Injection	50	5,000	5 g	38	42	Isotonic	250 mL	NDC 0409-7794-52

For the above Heparin Sodium products the pH range is 5.7 (5.0 to 6.0) and the osmolarity mOsmol/liter (calc.) is 304. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing.

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, 5.4)]*.

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 (5.7), Adverse Reactions (6)]*.

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 (7.2)]*.

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Hospira

LAB-0914-1.0

PRINCIPAL DISPLAY PANEL - 250 mL Bag Label - IM-5191

250 mL SINGLE-DOSE CONTAINER
NDC 0409-7793-52

HEPARIN

25,000 USP Units/250 mL
(100 USP Units/mL)

HEPARIN SODIUM IN
5% DEXTROSE INJECTION

WARNING: CONTAINS SULFITES
EACH 100 mL CONTAINS
HEPARIN SODIUM 10,000 USP
UNITS (PORCINE INTESTINAL
MUCOSA); DEXTROSE, HYDROUS
5 g; CITRIC ACID, ANHYDROUS
51 mg; SODIUM CITRATE,
DIHYDRATE 334 mg; SODIUM
METABISULFITE 20 mg;

STERILE. NOT MADE WITH
NATURAL RUBBER LATEX.
RECOMMENDED DOSAGE:
SEE PRESCRIBING INFORMATION.
ADDITIVES SHOULD NOT
BE MADE TO THIS SOLUTION.
SINGLE DOSE CONTAINER.
DISCARD UNUSED PORTION.
FOR INTRAVENOUS USE ONLY.

Rx ONLY

7
OTHER

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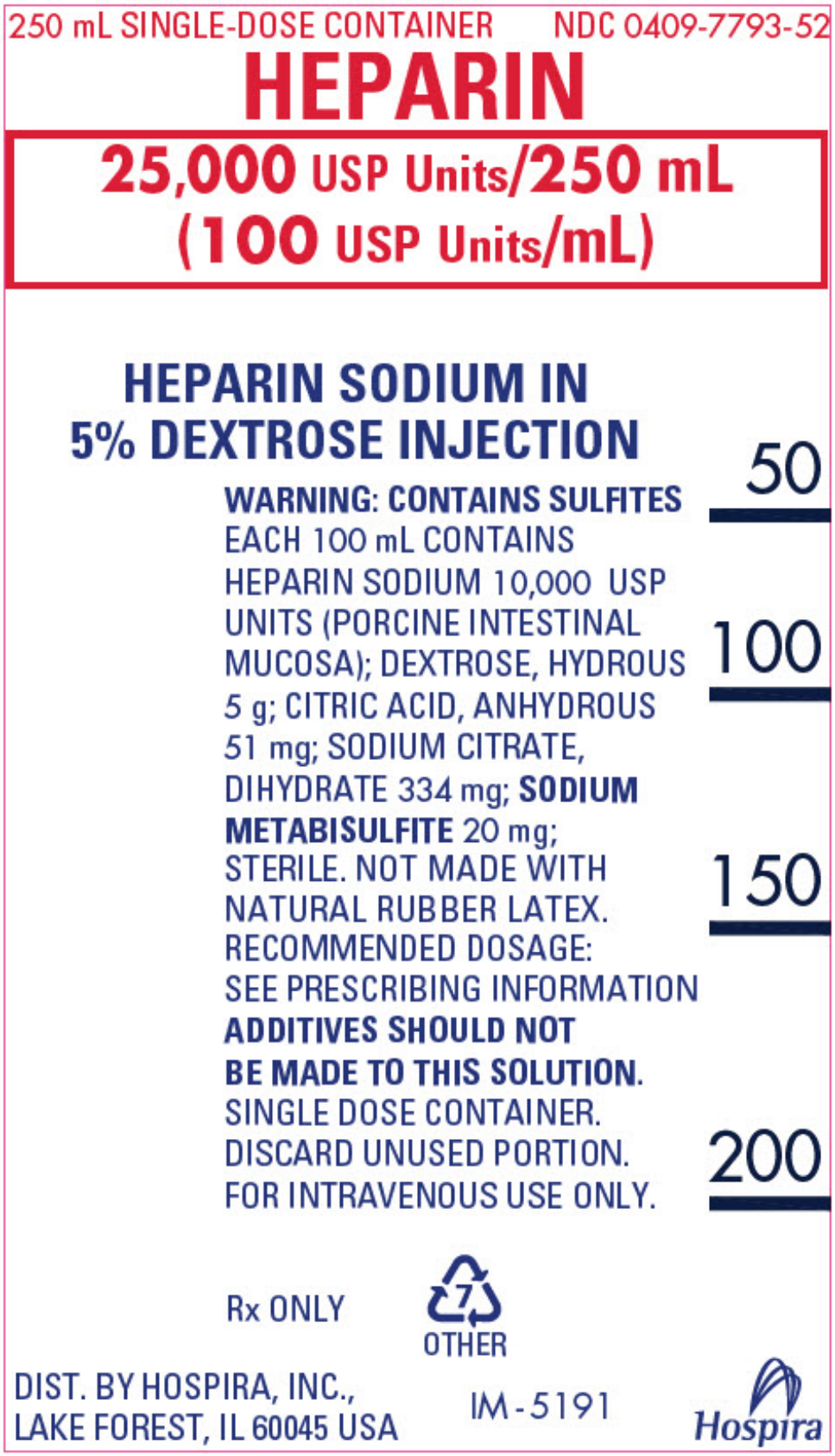
LAKE FOREST, IL 60045 USA
IM-5191
Hospira



PRINCIPAL DISPLAY PANEL - 100 mL Bag Label - IM-3956

100 mL SINGLE-DOSE CONTAINER
NDC 0409-7793-13

HEPARIN

Rx ONLY

10,000 USP Units/100 mL
(100 USP Units/mL)

HEPARIN SODIUM IN
5% DEXTROSE INJECTION
WARNING: CONTAINS SULFITES

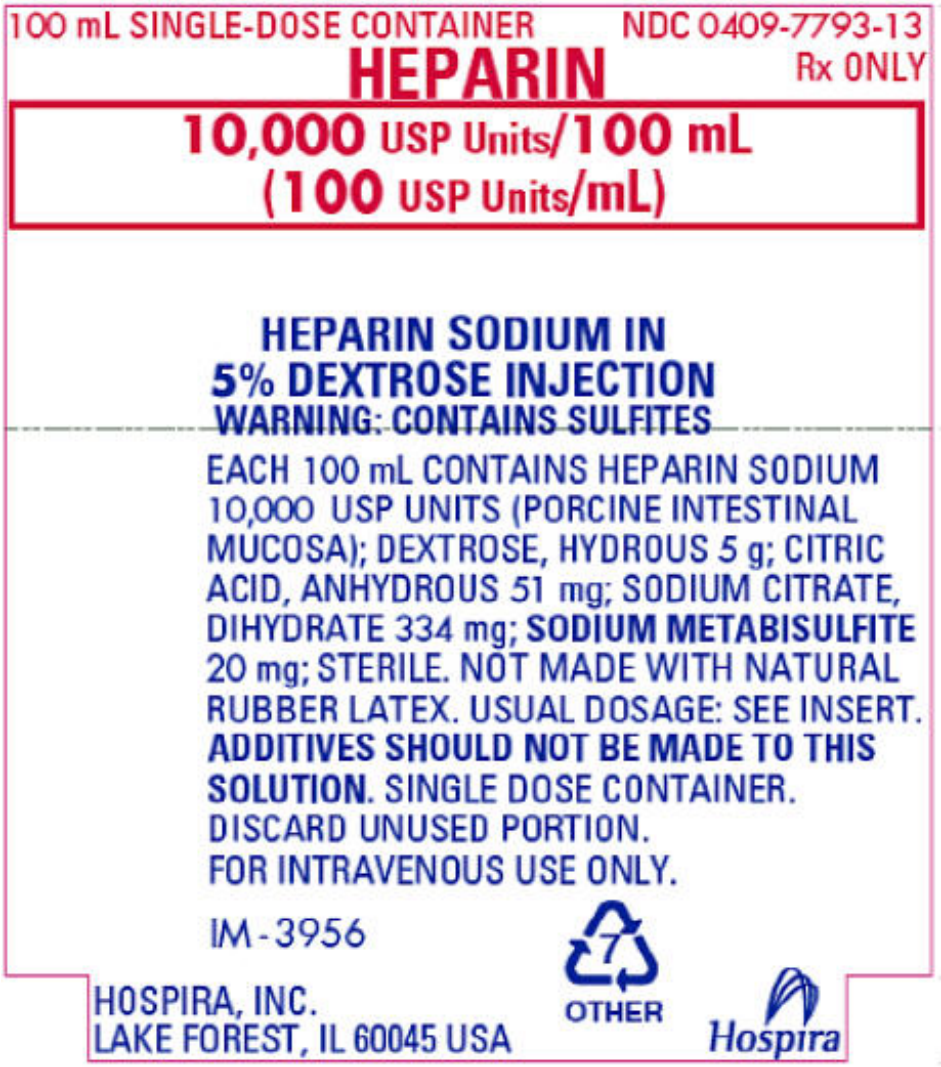
EACH 100 mL CONTAINS HEPARIN SODIUM 10,000 USP UNITS (PORCINE INTESTINAL MUCOSA); DEXTROSE, HYDROUS 5 g; CITRIC ACID, ANHYDROUS 51 mg; SODIUM CITRATE, DIHYDRATE 334 mg; **SODIUM METABISULFITE** 20 mg; STERILE. NOT MADE WITH NATURAL RUBBER LATEX. USUAL DOSAGE: SEE INSERT. **ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.** SINGLE DOSE CONTAINER. DISCARD UNUSED PORTION.
FOR INTRAVENOUS USE ONLY.

IM - 3956

HOSPIRA, INC.
LAKE FOREST, IL 60045 USA

7
OTHER

Hospira



PRINCIPAL DISPLAY PANEL - 100 mL Bag Label - WR-0482

TO OPEN – TEAR AT NOTCH

100 mL
SINGLE-DOSE
CONTAINER

HEPARIN
10,000 USP Units/100 mL
(100 USP Units/mL)

NDC 0409-7793-13

HEPARIN SODIUM
IN 5% DEXTROSE INJECTION

WARNING: CONTAINS SULFITES

Each 100 mL contains heparin sodium 10,000 USP Units (porcine intestinal mucosa); dextrose, hydrous 5 g; citric acid, anhydrous 51 mg; sodium citrate, dihydrate 334 mg; **sodium metabisulfite** 20 mg; Sterile. Not made with natural rubber latex. **Usual Dosage:** See insert. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.

Single Dose Container. Discard Unused Portion. For Intravenous Use Only.

Rx only

7
OTHER

F WR-0482

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Hospira

WINDOW AREA

TO OPEN – TEAR AT NOTCH

100 mL
SINGLE-DOSE
CONTAINER

HEPARIN

NDC 0409-7793-13

10,000 USP Units/100 mL
(100 USP Units/mL)

HEPARIN SODIUM IN 5% DEXTROSE INJECTION

(01)00304097793136

WARNING: CONTAINS SULFITES

Each 100 mL contains heparin sodium 10,000 USP Units (porcine intestinal mucosa); dextrose, hydrous 5 g; citric acid, anhydrous 51 mg; sodium citrate, dihydrate 334 mg; **sodium metabisulfite** 20 mg; Sterile. Not made with natural rubber latex. **Usual Dosage:** See insert. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.

Single Dose Container. Discard Unused Portion. For Intravenous Use Only.

Rx only

7
OTHER

F WR-0482

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MACHINE DIRECTION

HEPARIN

10,000 USP Units/100 mL
(100 USP Units/mL)

HEPARIN SODIUM IN 5% DEXTROSE INJECTION

B WR-0482

PRINCIPAL DISPLAY PANEL - 250 mL Bag Label - IM-5192

250 mL SINGLE-DOSE CONTAINER
NDC 0409-7794-52

HEPARIN

Rx ONLY

12,500 USP Units/250 mL
(50 USP Units/mL)

HEPARIN SODIUM IN
5% DEXTROSE INJECTION

WARNING: CONTAINS SULFITES
EACH 100 mL CONTAINS
HEPARIN SODIUM 5,000 USP
UNITS (PORCINE INTESTINAL
MUCOSA); DEXTROSE,
HYDROUS 5 g; CITRIC ACID,
ANHYDROUS 51 mg; SODIUM
CITRATE, DIHYDRATE 334 mg;
SODIUM METABISULFITE 20 mg;
STERILE. NOT MADE
WITH NATURAL RUBBER LATEX.
RECOMMENDED DOSAGE:
SEE PRESCRIBING INFORMATION.
ADDITIVES SHOULD
NOT BE MADE TO THIS
SOLUTION. SINGLE
DOSE CONTAINER. DISCARD
UNUSED PORTION. FOR
INTRAVENOUS USE ONLY.

7
OTHER

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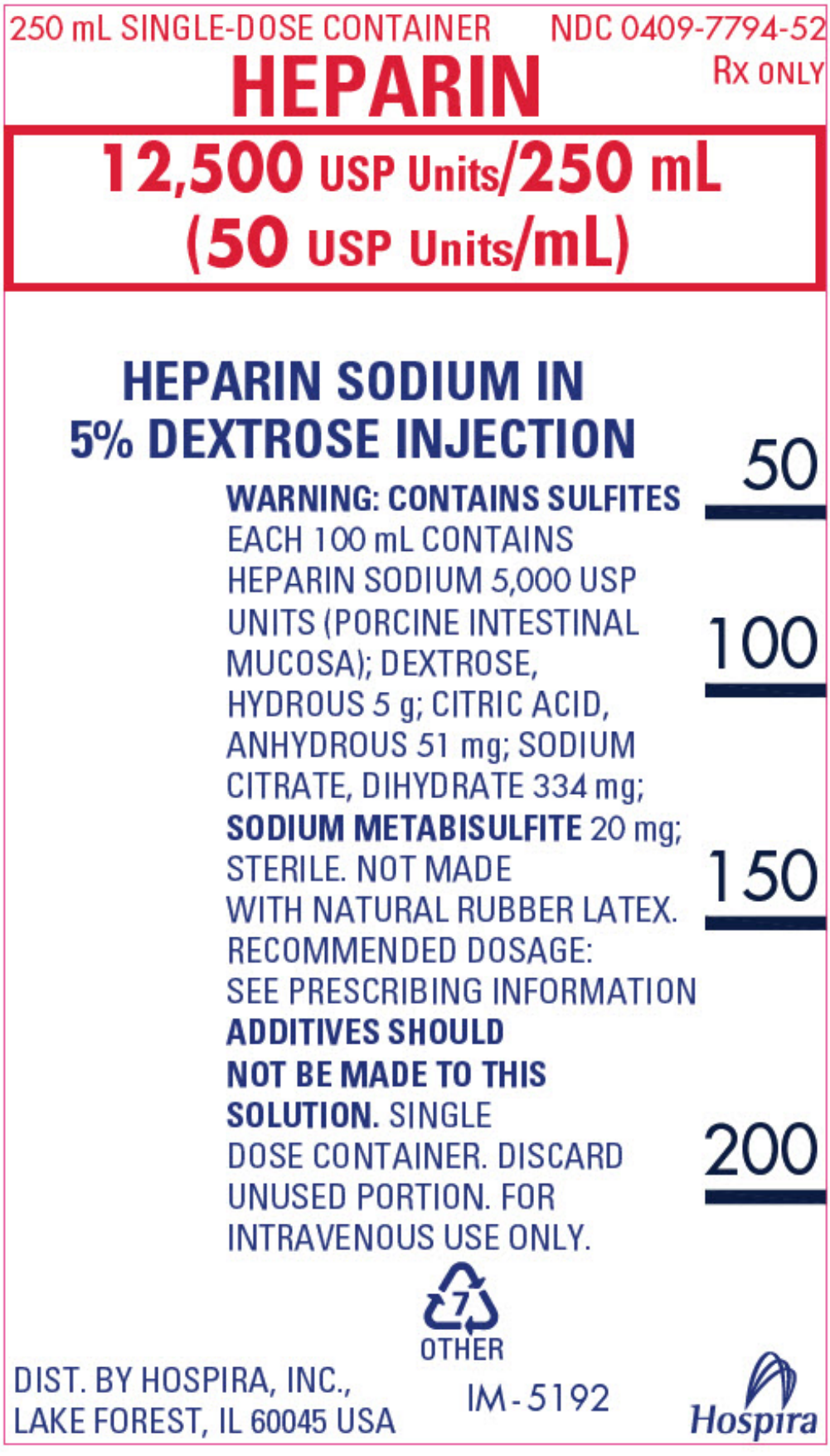
LAKE FOREST, IL 60045 USA
IM-5192
Hospira



HEPARIN SODIUM AND DEXTROSE

heparin sodium injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0409-7793
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HEPARIN SODIUM (UNII: ZZ45AB24CA) (HEPARIN - UNII:T2410KM04A)	HEPARIN	10000 [USP'U] in 100 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DEXTROSE MONOHYDRATE (UNII: LX22YL083G)	5 g in 100 mL
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	51 mg in 100 mL
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	334 mg in 100 mL
SODIUM METABISULFITE (UNII: 4VON5FNS3C)	20 mg in 100 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0409-7793-62	24 in 1 CASE	10/25/2005	
1		1 in 1 POUCH		
1	NDC:0409-7793-52	250 mL in 1 BAG; Type 0: Not a Combination Product		
2	NDC:0409-7793-23	24 in 1 CASE	02/09/2006	03/01/2010
2		1 in 1 POUCH		
2	NDC:0409-7793-13	100 mL in 1 BAG; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019339	10/25/2005	

HEPARIN SODIUM AND DEXTROSE

heparin sodium injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0409-7794
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HEPARIN SODIUM (UNII: ZZ45AB24CA) (HEPARIN - UNII:T2410KM04A)	HEPARIN	5000 [USP'U] in 100 mL

Inactive Ingredients	
Ingredient Name	Strength
DEXTROSE MONOHYDRATE (UNII: LX22YL083G)	5 g in 100 mL
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	51 mg in 100 mL
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	334 mg in 100 mL
SODIUM METABISULFITE (UNII: 4VON5FNS3C)	20 mg in 100 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0409-7794-62	24 in 1 CASE	06/13/2006	04/01/2015
1		1 in 1 POUCH		
1	NDC:0409-7794-52	250 mL in 1 BAG; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019339	06/13/2006	04/01/2015

Labeler - Hospira, Inc. (141588017)

Establishment

Name	Address	ID/FEI	Business Operations
Hospira, Inc.		827731089	ANALYSIS(0409-7793, 0409-7794)

Establishment

Name	Address	ID/FEI	Business Operations
Hospira, Inc.		093132819	ANALYSIS(0409-7793, 0409-7794) , LABEL(0409-7793, 0409-7794) , MANUFACTURE(0409-7793, 0409-7794) , PACK(0409-7793, 0409-7794)

Establishment

Name	Address	ID/FEI	Business Operations
Hospira, Inc.		030606222	ANALYSIS(0409-7793, 0409-7794)

Revised: 4/2020 Hospira, Inc.