Intravenous Solutions with Heparin Sodium Injection

20,000 USP Units/500 mL (40 USP Units/mL) or 25,000 USP Units/500 mL (50 USP Units/mL) of Heparin Sodium in 5% Dextrose Injection

Flexible Plastic Container
Do not admix with other drugs.

DESCRIPTION
 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 or 5,000 USP Units; dextrose, hydrous 5 g; citric acid, anhydrous 51 mg and dibasic sodium phosphate, anhydrous 103 mg added as buffers; sodium metabisulfite added, 20 mg as an antioxidant. Each liter contains the following electrolytes: Sodium 17 mEq; phosphate 15 mEq and citrate 8 mEq. May contain citric acid for pH adjustment. See Table for summary of contents and characteristics of these solutions. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

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.

The flexible plastic container is fabricated from a specially formulated polyvinyl chloride. 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.

**CLINICAL PHARMACOLOGY**

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.

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.

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.

Peak plasma levels of heparin are achieved 2 to 4 hours following subcutaneous administration, although there are considerable individual variations. 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 (t½ = 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.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

**INDICATIONS AND USAGE**

Heparin sodium is indicated for:

Atrial fibrillation with embolization;
Treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation);
Prevention of clotting in arterial and heart surgery;
Prophylaxis and treatment of peripheral arterial embolism;
As an anticoagulant in extracorporeal arterial circulation and dialysis procedures.

**CONTRAINDICATIONS**

Heparin sodium should not be used in patients:

With severe thrombocytopenia;
With a known hypersensitivity to heparin or pork products (e.g., anaphylactoid reactions) (See **ADVERSE REACTIONS, Hypersensitivity**);
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);
With an uncontrollable active bleeding state (See WARNINGS), except when this is due to disseminated intravascular coagulation.
Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

**WARNINGS**
Heparin is not intended for intramuscular use

**Hypersensitivity:**
Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. (See ADVERSE REACTIONS, Hypersensitivity.)

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.

**Hemorrhage:**
Hemorrhage can occur at virtually any site in patients receiving heparin. 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. Some of the conditions in which increased danger of hemorrhage exists are:
- **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.
- **Gastrointestinal** — Ulcerative lesions and continuous tube drainage of the stomach or small intestine.
- **Other** — Menstruation, liver disease with impaired hemostasis.

**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, heparin should be discontinued promptly (See OVERDOSAGE).

**Thrombocytopenia:**
Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of up to 30%. 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 Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis)), the heparin product should be discontinued, and, if necessary, an alternative anticoagulant administered.

**Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis):**
HIT is a serious immune-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as HIT with thrombosis. 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.

Immune-mediated HIT is diagnosed based on clinical findings supplemented by laboratory tests confirming the presence of antibodies to heparin sodium, or platelet activation induced by heparin sodium. A drop in platelet count greater than 50% from baseline is considered indicative of HIT. Platelet counts begin to fall 5 to 10 days after exposure to heparin sodium in heparin sodium-naïve individuals, and reach a threshold by days 7 to 14. In contrast, “rapid onset” HIT can occur very quickly (within 24 hours following heparin sodium initiation), especially in patients with a recent exposure to heparin sodium (i.e. previous 3 months). Thrombosis development shortly after documenting thrombocytopenia is a characteristic finding in almost half of all patients with HIT.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³ 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 (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).

**Other:**
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.

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.

Solutions containing dextrose without electrolytes should not be administered simultaneously with blood through the same infusion set because of the possibility of agglomeration.

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

Because dosages of this drug are titrated to response (See DOSAGE AND ADMINISTRATION), no additives should be made to Heparin Sodium in 5% Dextrose Injection.

**PRECAUTIONS**

**General**

a. **Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) (With or Without Thrombosis) and Delayed Onset of HIT (With or Without Thrombosis):** (See WARNINGS.)

b. **Heparin Resistance:**
   Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

c. **Increased Risk to Older Patients, Especially Women:**
   A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.
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.

Solutions containing dextrose should be used with caution in patients with overt or known subclinical diabetes mellitus, or carbohydrate intolerance for any reason.

Do not use plastic container in series connection.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

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.

**Laboratory Tests**

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

**Drug Interactions**

**Oral Anticoagulants:** Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose 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.

**Other Interactions:** Digitalis, tetracyclines, nicotine, antihistamines, or IV 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.

**Drug/Laboratory Test Interactions**

**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 amino-transferase 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.

**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 with Heparin Sodium in 5% Dextrose Injection.

**Pregnancy**

**Pregnancy Category C**

There are no adequate and well-controlled studies on heparin use in pregnant women. In published reports, heparin exposure during pregnancy did not show evidence of an increased risk of adverse maternal or fetal outcomes in humans. Heparin sodium does not cross the placenta, based on human and animal studies. Administration of heparin to pregnant animals at doses higher than the maximum human
daily dose based on body weight resulted in increased resorptions. Use heparin sodium during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 human daily dose based on body weight. The number of early resorptions increased in both species. There was no evidence of teratogenic effects.

Nursing Mothers
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. Exercise caution when administering Heparin Sodium to a nursing mother.

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, Pediatric Use).

Geriatric Use
A higher incidence of bleeding has been reported in patients over 60 years of age, especially women (See PRECAUTIONS, General). Clinical studies indicate that lower doses of heparin may be indicated in these patients (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Hemorrhage:
Hemorrhage is the chief complication that may result from heparin therapy (See WARNINGS). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (See OVERDOSAGE). 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 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.)

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.)
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.

**Miscellaneous:**
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.

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.

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.

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

**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 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 labeling of Protamine Sulfate Injection, USP products should be consulted.

**DOSAGE AND ADMINISTRATION**
Heparin sodium is not effective by oral administration and these premixed formulations should be given by intermittent intravenous injection or intravenous infusion.

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, regardless of the route of administration.
Converting to Oral Anticoagulant

When an oral anticoagulant of the coumarin or similar type is to be begun in patients already receiving heparin sodium, baseline and subsequent tests of prothrombin activity must be determined at a time when heparin activity is too low to affect the prothrombin time. This is about 5 hours after the last IV bolus. If continuous IV heparin infusion is used, prothrombin time can usually be measured at any time.

In converting from heparin to an oral anticoagulant, the dose of the oral anticoagulant should be the usual initial amount and thereafter prothrombin time should be determined at the usual intervals. To ensure continuous anticoagulation, it is advisable to continue full heparin therapy for several days after the prothrombin time has reached the therapeutic range. Heparin therapy may then be discontinued without tapering.

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>
<thead>
<tr>
<th>Method of Administration</th>
<th>Frequency</th>
<th>Recommended Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>Initial Dose</td>
<td>10,000 Units, either undiluted or in 50 – 100 mL of 5% Dextrose Injection</td>
</tr>
<tr>
<td>Intravenous Injection</td>
<td>Every 4 to 6 hours</td>
<td>5,000 – 10,000 Units, either undiluted or in 50 – 100 mL of 5% Dextrose Injection</td>
</tr>
<tr>
<td>Continuous Intravenous</td>
<td>Initial Dose</td>
<td>5,000 Units by IV injection</td>
</tr>
<tr>
<td>Infusion</td>
<td>Continuous</td>
<td>20,000 – 40,000 Units/24 hours in 1000 mL of 5% Dextrose Injection</td>
</tr>
</tbody>
</table>

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

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 (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/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.

Geriatric Use

Patients over 60 years of age may require lower doses of heparin. (See PRECAUTIONS).

- 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.
INSTRUCTIONS FOR USE

To Open
Tear outer wrap at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Preparation for Administration
(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.

HOW SUPPLIED
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:

<table>
<thead>
<tr>
<th>Unit of Sale</th>
<th>Product</th>
<th>Heparin Sodium (USP Units/mL)</th>
<th>Heparin Sodium (USP Units)</th>
<th>Dextrose (hydr. g)</th>
<th>Tonicity</th>
<th>Solution Volume</th>
<th>Each</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC 0409-7760-03</td>
<td>Heparin Sodium 20,000 USP Units/500 mL (40 USP Units/mL) in 5% Dextrose Injection</td>
<td>40</td>
<td>4,000</td>
<td>5</td>
<td>Isotonic</td>
<td>500 mL</td>
<td>NDC 0409-7760-13</td>
</tr>
<tr>
<td>Carton of 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDC 0409-7761-03</td>
<td>Heparin Sodium 25,000 USP Units/500 mL (50 USP Units/mL) in 5% Dextrose Injection</td>
<td>50</td>
<td>5,000</td>
<td>5</td>
<td>Isotonic</td>
<td>500 mL</td>
<td>NDC 0409-7761-13</td>
</tr>
<tr>
<td>Carton of 24</td>
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</table>

For the above Heparin Sodium products the pH range is 5.2 to 6.0 and the osmolarity mOsmol/liter (calc.) is 287.

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

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Hospira, Inc., Lake Forest, IL 60045 USA