

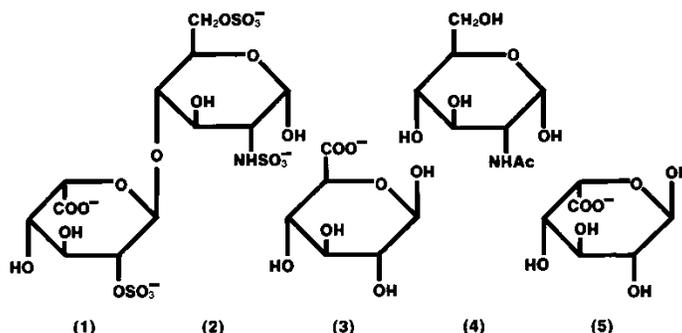
Heparin Sodium Injection, USP

Rx only

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.

Structural formula of Heparin Sodium (representative sub-units):



Heparin Sodium Injection, USP is a sterile solution of heparin sodium derived from porcine intestinal mucosa, standardized for anticoagulant activity. It is to be administered by intravenous or deep subcutaneous routes. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

Heparin Sodium Injection, USP is available in the following concentrations/mL:

Heparin Sodium	Sodium Chloride	Benzyl Alcohol
1,000 USP units	8.6 mg	0.01 mL
5,000 USP units	7 mg	0.01 mL
10,000 USP units	5 mg	0.01 mL

pH 5.0-7.5; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment.

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 ($t_{1/2}=10$ min.) 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 Injection is indicated for:

Anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension;

Low-dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominothoracic surgery or who, for other reasons, are at risk of developing thromboembolic disease (see **DOSAGE AND ADMINISTRATION**);

Prophylaxis and treatment of pulmonary embolism;

Atrial fibrillation with embolization;

Diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation);

Prevention of clotting in arterial and cardiac surgery;

Prophylaxis and treatment of peripheral arterial embolism.

Heparin may also be employed as an anticoagulant in blood transfusions, extracorporeal circulation, and dialysis procedures and in blood samples for laboratory purposes.

CONTRAINDICATIONS

Heparin sodium should NOT be used in patients with the following conditions:

Severe thrombocytopenia;

When 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);

An uncontrolled active bleeding state (see **WARNINGS**), except when this is due to disseminated intravascular coagulation.

WARNINGS

Heparin is not intended for intramuscular use.

Fatal Medication Errors

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

Hypersensitivity

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

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 sodium should be promptly discontinued. (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 $100,000/\text{mm}^3$) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below $100,000/\text{mm}^3$ 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, 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 sodium should be evaluated for HIT (with or without thrombosis).

Use in Neonates

This product contains the preservative benzyl alcohol and is not recommended for use in neonates. There have been reports of fatal ‘gaspings syndrome’ in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Carefully examine all Heparin Sodium Injection vials to confirm choice of the correct strength prior to administration of the drug. Pediatric patients, including neonates, have died as a result of medication errors in which Heparin Sodium Injection vials have been confused with “catheter lock flush” vials. (See **WARNINGS, Fatal Medication Errors.**)

PRECAUTIONS

General

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

See **WARNINGS.**

Heparin Resistance

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

Increased Risk to Older Patients, Especially Women

A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

Laboratory Tests

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. (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 or 24 hours after the last subcutaneous dose should elapse before blood is drawn, if a valid prothrombin time is to be obtained.

Platelet Inhibitors

Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other Interactions

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.

Drug/Laboratory Tests Interactions

Hyperaminotransferasemia

Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) 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, increases that might be caused by drugs (like heparin) should be interpreted with caution.

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.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects

Heparin does not cross the placental barrier.

Nursing Mothers

Heparin is not excreted in human milk.

Pediatric Use

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 side of the feet, may occur. (See **Warnings, Precautions.**)

Certain episodes of painful, ischemic and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia-associated complications remains to be determined.

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 (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.

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 consult the labeling of Protamine Sulfate Injection, USP products.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency.

Confirm the choice of the correct Heparin Sodium Injection vial prior to administration of the drug to a patient. (See WARNINGS, Fatal Medication Errors.) The 1 mL vial must not be confused with a “catheter lock flush” vial or other 1 mL vial of inappropriate strength. To lessen this risk, the 1 mL vial includes a red cautionary label that extends above the main label. Read the cautionary statement and confirm that you have selected the correct medication and strength. Then locate the “Tear Here” point on the label, and remove this red cautionary label prior to removing the flip-off cap.

When heparin is added to an infusion solution for continuous intravenous administration, the container should be inverted at least six times to ensure adequate mixing and prevent pooling of the heparin in the solution.

Heparin sodium is not effective by oral administration and should be given by intermittent intravenous injection, intravenous infusion, or deep subcutaneous (intrafat, i.e., above the iliac crest or abdominal fat layer) injection. **The intramuscular route of administration should be avoided because of the frequent occurrence of hematoma at the injection site.**

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. After deep subcutaneous (intrafat) injections, tests for adequacy of dosage are best performed on samples drawn 4 to 6 hours after the injection.

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 intravenous bolus and 24 hours after the last subcutaneous dose. 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.

Therapeutic Anticoagulant Effect With Full-Dose Heparin

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:

METHOD OF ADMINISTRATION	FREQUENCY	RECOMMENDED DOSE [based on 150 lb (68 kg) patient]
Deep Subcutaneous (Intrafat) Injection	Initial dose	5,000 units by IV injection, followed by 10,000 to 20,000 units of a concentrated solution, subcutaneously
	Every 8 hours	8,000 to 10,000 units of a concentrated solution
	or Every 12 hours	15,000 to 20,000 units of a concentrated solution
Intermittent Intravenous Injection	Initial dose	10,000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, USP
	Every 4 to 6 hours	5,000 to 10,000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, USP

METHOD OF ADMINISTRATION	FREQUENCY	RECOMMENDED DOSE [based on 150 lb (68 kg) patient]
Intravenous Infusion	Initial dose	5,000 units by IV injection
	Continuous	20,000 to 40,000 units/24 hours in 1000 mL of 0.9% Sodium Chloride Injection, USP (or in any compatible solution) for infusion

Pediatric Use

Follow recommendations of appropriate pediatric reference texts. In general, the following dosage schedule may be used as a guideline:

Initial Dose

50 units/kg (IV, drip)

Maintenance Dose

100 units/kg (IV, drip) every 4 hours, or 20,000 units/m²/24 hours continuously

Geriatric Use

Patients over 60 years of age may require lower doses of heparin.

Surgery of the Heart and Blood Vessels

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

Low-Dose Prophylaxis of Postoperative Thromboembolism

A number of well-controlled clinical trials have demonstrated that low-dose heparin prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep vein thrombosis in the legs (as measured by the I-125 fibrinogen technique and venography) and of clinical pulmonary embolism. The most widely used dosage has been 5,000 units 2 hours before surgery and 5,000 units every 8 to 12 hours thereafter for 7 days or until the patient is fully ambulatory, whichever is longer. The heparin is given by deep subcutaneous injection in the arm or abdomen with a fine needle (25- to 26-gauge) to minimize tissue trauma. A concentrated solution of heparin sodium is recommended. Such prophylaxis should be reserved for patients over the age of 40 who are undergoing major surgery. Patients with bleeding disorders and those

having neurosurgery, spinal anesthesia, eye surgery or potentially sanguineous operations should be excluded, as should patients receiving oral anticoagulants or platelet-active drugs (see **WARNINGS**). The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or postoperatively should be borne in mind. If such bleeding occurs, discontinuance of heparin and neutralization with protamine sulfate are advisable. If clinical evidence of thromboembolism develops despite low-dose prophylaxis, full therapeutic doses of anticoagulants should be given unless contraindicated. All patients should be screened prior to heparinization to rule out bleeding disorders, and monitoring should be performed with appropriate coagulation tests just prior to surgery. Coagulation test values should be normal or only slightly elevated. There is usually no need for daily monitoring of the effect of low-dose heparin in patients with normal coagulation parameters.

Extracorporeal Dialysis

Follow equipment manufacturers' operating directions carefully.

Blood Transfusion

Addition of 400 to 600 USP units per 100 mL of whole blood is usually employed to prevent coagulation. Usually, 7,500 USP units of heparin sodium are added to 100 mL of 0.9% Sodium Chloride Injection, USP (or 75,000 USP units per 1000 mL of 0.9% Sodium Chloride Injection, USP) and mixed; from this sterile solution, 6 to 8 mL are added per 100 mL of whole blood.

Laboratory Samples

Addition of 70 to 150 units of heparin sodium per 10 to 20 mL sample of whole blood is usually employed to prevent coagulation of the sample. Leukocyte counts should be performed on heparinized blood within 2 hours after addition of the heparin. Heparinized blood should not be used for isoagglutinin, complement, or erythrocyte fragility tests or platelet counts.

HOW SUPPLIED

Heparin Sodium Injection, USP

1,000 USP units/mL

1 mL vial packaged in 25s (NDC 0641-0391-12)

10 mL Multiple Dose vial packaged in 25s (NDC 0641-2440-55)

30 mL Multiple Dose vial packaged in 25s (NDC 0641-2450-55)

5,000 USP units/mL

1 mL vial packaged in 25s (NDC 0641-0400-12)

10 mL Multiple Dose vial packaged in 25s (NDC 0641-2460-55)

10,000 USP units/mL

1 mL vial packaged in 25s (NDC 0641-0410-12)

4 mL Multiple Dose vial packaged in 25s (NDC 0641-2470-55)

Storage

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

REFERENCES

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