

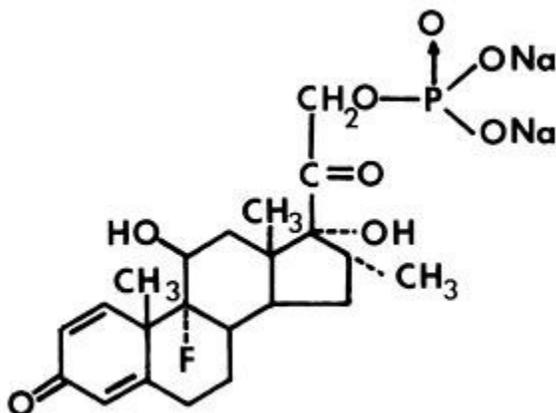
DEXAMETHASONE SODIUM PHOSPHATE - dexamethasone sodium phosphate injection

Baxter Healthcare Corporation

DESCRIPTION

Dexamethasone sodium phosphate, a synthetic adrenocortical steroid, is a white or slightly yellow crystalline powder. It is freely soluble in water and is exceedingly hygroscopic. The molecular weight is 516.41. It is designated chemically as 9-fluoro-11 β ,17-dihydroxy-16 α -methyl-21-(phosphonoxy)pregna-1,4-diene-3, 20-dione disodium salt.

The molecular formula is: C₂₂H₂₈FN₂O₈P and the structural formula is:



Dexamethasone Sodium Phosphate Injection is a sterile solution of dexamethasone sodium phosphate for intravenous and intramuscular use. The 4 mg/mL strength may also be used for intra-articular, intralesional and soft tissue administration.

Each mL of Dexamethasone Sodium Phosphate Injection 4 mg/mL contains dexamethasone sodium phosphate, equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone. Inactive ingredients per mL: 1 mg sodium sulfite anhydrous, 19.4 mg sodium citrate anhydrous and 10.42 mg (0.01 mL) benzyl alcohol (preservative) in Water for Injection.

Each mL of Dexamethasone Sodium Phosphate Injection 10 mg/mL contains dexamethasone sodium phosphate, equivalent to 10 mg dexamethasone phosphate or 8.33 mg dexamethasone. Inactive ingredients per mL: 1.5 mg sodium sulfite anhydrous, 16.5 mg sodium citrate anhydrous and 10.42 mg (0.01 mL) benzyl alcohol (preservative) in Water for Injection.

The pH of both concentrations is 7.0-8.5; sodium hydroxide and/or citric acid used, if needed, for pH adjustment. Sealed under nitrogen.

CLINICAL PHARMACOLOGY

Dexamethasone sodium phosphate injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

A. By Intravenous or Intramuscular Injection When Oral Therapy is not Feasible:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance)

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful

Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected

Congenital adrenal hyperplasia

Nonsuppurative thyroiditis

Hypercalcemia associated with cancer

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Post-traumatic osteoarthritis

Synovitis of osteoarthritis

Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

Acute and subacute bursitis

Epicondylitis

Acute nonspecific tenosynovitis

Acute gouty arthritis

Psoriatic arthritis

Ankylosing spondylitis

3. Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus

Acute rheumatic carditis

4. Dermatologic Diseases

Pemphigus

Severe erythema multiforme (Stevens-Johnson syndrome)

Exfoliative dermatitis

Bullous dermatitis herpetiformis

Severe seborrheic dermatitis

Severe psoriasis

Mycosis fungoides

5. Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma

Contact dermatitis

Atopic dermatitis

Serum sickness

Seasonal or perennial allergic rhinitis

Drug hypersensitivity reactions

Urticarial transfusion reactions

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)

6. Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus

Iritis, iridocyclitis

Chorioretinitis

Diffuse posterior uveitis and choroiditis

Optic neuritis

Sympathetic ophthalmia

Anterior segment inflammation

Allergic conjunctivitis

Keratitis

Allergic corneal marginal ulcers

7. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

Ulcerative colitis (Systemic therapy)

Regional enteritis (Systemic therapy)

8. Respiratory Diseases

Symptomatic sarcoidosis

Berylliosis

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy

Loeffler's syndrome not manageable by other means

Aspiration pneumonitis

9. Hematologic Disorders

Acquired (autoimmune) hemolytic anemia

Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)

Secondary thrombocytopenia in adults

Erythroblastopenia (RBC anemia)

Congenital (erythroid) hypoplastic anemia

10. Neoplastic Diseases

For palliative management of:

Leukemias and lymphomas in adults

Acute leukemia of childhood

11. Edematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type, or that due to lupus erythematosus

12. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy

Trichinosis with neurologic or myocardial involvement

13. Diagnostic Testing Of Adrenocortical Hyperfunction

14. Cerebral Edema associated with primary or metastatic brain tumor, craniotomy or head injury. Use in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

B. By Intra-Articular or Soft Tissue Injection

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Synovitis of osteoarthritis

Rheumatoid arthritis

Acute and subacute bursitis

Acute gouty arthritis

Epicondylitis

Acute nonspecific tenosynovitis

Post-traumatic osteoarthritis

C. By Intralesional Injection

Keloids

Localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis)

Discoid lupus erythematosus

Necrobiosis lipoidica diabetorum

Alopecia areata

May also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Systemic fungal infections (see WARNINGS regarding amphotericin B).

Hypersensitivity to any component of this product, including sulfites (see WARNINGS).

WARNINGS

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Anaphylactoid and hypersensitivity reactions have been reported for Dexamethasone Sodium Phosphate Injection (see ADVERSE REACTIONS).

Dexamethasone Sodium Phosphate Injection contains sodium sulfite, 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.

Corticosteroids may exacerbate systemic fungal infections and, therefore, should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infections when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false-negative results.

In cerebral malaria, a double blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is unknown. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pool intramuscular immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

The use of Dexamethasone Sodium Phosphate Injection in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis. Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Usage in Pregnancy

Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that antacids be administered between meals to help prevent peptic ulcer.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine and rifampin may enhance the metabolic clearance of corticosteroids resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever and malaise is suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided.

Corticosteroids should not be injected into unstable joints.

Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Frequent intra-articular injection may result in damage to joint tissues.

The slower rate of absorption by intramuscular administration should be recognized.

Information for Patients

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles.

Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

Sodium retention

Fluid retention

Congestive heart failure in susceptible patients

Potassium loss

Hypokalemic alkalosis

Hypertension

Musculoskeletal

Muscle weakness

Steroid myopathy

Loss of muscle mass

Osteoporosis

Vertebral compression fractures

Aseptic necrosis of femoral and humeral heads

Pathologic fracture of long bones

Tendon rupture

Gastrointestinal

Peptic ulcer with possible subsequent perforation and hemorrhage

Perforation of the small and large bowel, particularly in patients with inflammatory bowel disease

Pancreatitis

Abdominal distention

Ulcerative esophagitis

Dermatologic

Impaired wound healing

Thin, fragile skin

Petechiae and ecchymoses

Erythema

Increased sweating

May suppress reactions to skin tests

Burning or tingling, especially in the perineal area (after IV injection)

Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema

Neurologic

Convulsions

Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment

Vertigo

Headache

Psychic disturbances

Endocrine

Menstrual irregularities

Development of cushingoid state

Suppression of growth in children

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetics

Hirsutism

Ophthalmic

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Metabolic

Negative nitrogen balance due to protein catabolism

Cardiovascular

Myocardial rupture following recent myocardial infarction (see WARNINGS)

Other

Anaphylactoid or hypersensitivity reactions

Thromboembolism

Weight gain

Increased appetite

Nausea

Malaise

Hiccups

The following *additional* adverse reactions are related to parenteral corticosteroid therapy:

Rare instances of blindness associated with intralesional therapy around the face and head

Hyperpigmentation or hypopigmentation

Subcutaneous and cutaneous atrophy

Sterile abscess

Postinjection flare (following intra-articular use)

Charcot-like arthropathy

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

The oral LD₅₀ of dexamethasone in female mice was 6.5 g/kg. The intravenous LD₅₀ of dexamethasone sodium phosphate in female mice was 794 mg/kg.

DOSAGE AND ADMINISTRATION

Dexamethasone Sodium Phosphate Injection, 4 mg/mL-*For intravenous, intramuscular, intra-articular, intralesional and soft tissue injection.*

Dexamethasone Sodium Phosphate Injection, 10 mg/mL-*For intravenous and intramuscular injection only.*

Dexamethasone Sodium Phosphate Injection can be given directly from the vial or it can be added to Sodium Chloride Injection or Dextrose Injection and administered by intravenous drip.

Solutions used for intravenous administration or further dilution of this product should be preservative-free when used in the neonate, especially the premature infant.

When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

INTRAVENOUS AND INTRAMUSCULAR INJECTION

The initial dosage of Dexamethasone Sodium Phosphate Injection varies from 0.5 to 9 mg a day depending on the disease being treated. In less severe diseases doses lower than 0.5 mg may suffice, while in severe diseases doses higher than 9 mg may be required. The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue Dexamethasone Sodium Phosphate Injection and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness and the effect of stress (e.g., surgery, infection, trauma).

During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

When the intravenous route of administration is used, dosage usually should be the same as the oral dosage. In certain overwhelming, acute, life-threatening situations, however, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages. The slower rate of absorption by intramuscular administration should be recognized.

Shock

There is a tendency in current medical practice to use high (pharmacologic) doses of corticosteroids for the treatment of unresponsive shock. The following dosages of Dexamethasone Sodium Phosphate Injection have been suggested by various authors:

Author*	Dosage
Cavanagh ¹	3 mg/kg of body weight per 24 hours by constant intravenous infusion after an initial intravenous injection of 20 mg
Dietzman ²	2 to 6 mg/kg of body weight as a single intravenous injection
Frank ³	40 mg initially followed by repeat intravenous injection every 4 to 6 hours while shock persists
Oaks ⁴	40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists
Schumer ⁵	1 mg/kg of body weight as a single intravenous injection

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized and usually not longer than 48 to 72 hours.

Although adverse reactions associated with high dose, short term corticosteroid therapy are uncommon, peptic ulceration may occur.

Cerebral Edema

Dexamethasone Sodium Phosphate Injection is generally administered initially in a dosage of 10 mg intravenously followed by four mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with two mg two or three times a day may be effective.

Acute Allergic Disorders

In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone Sodium Phosphate Injection, 4 mg/mL -*First day*, 1 or 2 mL (4 or 8 mg) intramuscularly.

Dexamethasone tablets, 0.75 mg - *Second and third days*, 4 tablets in two divided doses each day; *fourth day* 2 tablets in two divided doses; *fifth and sixth days*, 1 tablet each day; *seventh day*, no treatment; *eighth day*, follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

Intra-articular, Intralesional and Soft Tissue Injection

Intra-articular, intralesional and soft tissue injections are generally employed when the affected joints or areas are limited to one or two sites. Dosage and frequency of injection varies depending on the condition and the site of injection. The usual dose is from 0.2

to 6 mg. The frequency usually ranges from once every three to five days to once every two to three weeks. Frequent intra-articular injection may result in damage to joint tissues. Some of the usual single doses are:

<u>Site of Injection</u>	<u>Amount of Dexamethasone Phosphate (mg)</u>
Large Joints (e.g., knee)	2 to 4
Small Joints (e.g., Interphalangeal, Temporomandibular)	0.8 to 1
Bursae	2 to 3
Tendon Sheaths	0.4 to 1
Soft Tissue Infiltration	2 to 6
Ganglia	1 to 2

Dexamethasone Sodium Phosphate Injection is particularly recommended for use in conjunction with one of the less soluble, longer-acting steroids for intra-articular and soft tissue injection.

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

HOW SUPPLIED

Dexamethasone Sodium Phosphate Injection, USP is available in the following package:

10 mg/mL

1 mL DOSETTE vials packaged in 25s (NDC 0641-0367-25)

Storage

Protect from light: Keep covered in carton until time of use. Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Avoid freezing. Do not use if solution is hazy or has a precipitate. Do not autoclave.

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