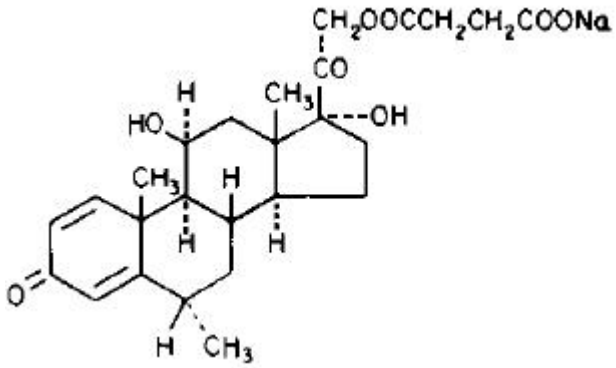
SOLU-MEDROL®
methylprednisolone sodium succinate
for injection, USP

For Intravenous or Intramuscular Administration

DESCRIPTION

SOLU-MEDROL Sterile Powder contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate, USP, occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

The chemical name for methylprednisolone sodium succinate is pregna-1,4-diene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-6-methyl-monosodium salt, (6α, 11β), and the molecular weight is 496.53. The structural formula is represented below:



Methylprednisolone sodium succinate is so extremely soluble in water that it may be administered in a small volume of diluent and is especially well suited for intravenous use in situations in which high blood levels of methylprednisolone are required rapidly.

SOLU-MEDROL is available in several strengths and packages for intravenous or intramuscular administration.

40 mg Act-O-Vial® System (Single-Dose Vial)—Each mL (when mixed) contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; 17.46 mg dibasic sodium phosphate dried; and 25 mg lactose hydrous.

125 mg Act-O-Vial System (Single-Dose Vial)—Each 2 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; and 17.4 mg dibasic sodium phosphate dried.

500 mg Vial—Each 8 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; 69.6 mg dibasic sodium phosphate dried.

500 mg Act-O-Vial System (Single-Dose Vial)—Each 4 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; and 69.6 mg dibasic sodium phosphate dried.

1 gram Vial—Each 16 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 1 gram methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried.

1 gram Act-O-Vial System (Single-Dose Vial)—Each 8 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 1 gram methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; and 139.2 mg dibasic sodium phosphate dried.

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8 and the tonicities are, for the 40 mg per mL solution, 0.50 osmolar; for the 125 mg per 2 mL, 500 mg per 8 mL and 1 gram per 16 mL solutions, 0.40 osmolar; for the 1 gram per 8 mL solution, 0.44 osmolar. (Isotonic saline = 0.28 osmolar).

IMPORTANT — Use only the accompanying diluent
when reconstituting SOLU-MEDROL.
Use within 48 hours after mixing

ACTIONS

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs 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.

Methylprednisolone is a potent anti-inflammatory steroid with greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of SOLU-MEDROL Sterile Powder and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to

one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

INDICATIONS

When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the condition, SOLU-MEDROL Sterile Powder is indicated for intravenous or intramuscular use in the following conditions:

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
   Systemic dermatomyositis (polymyositis)
   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
   Drug hypersensitivity reactions
   Urticarial transfusion reactions

Atopic dermatitis
Serum sickness
Seasonal or perennial allergic rhinitis
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
   Allergic corneal marginal ulcers
   Keratitis
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. **Nervous System**
    Acute exacerbations of multiple sclerosis
13. **Miscellaneous**
    Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
    Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS

SOLU-MEDROL Sterile Powder is contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS

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

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2]

A study has failed to establish the efficacy of SOLU-MEDROL in the treatment of sepsis syndrome and septic shock. The study also suggests that treatment of these conditions with SOLU-MEDROL may increase the risk of mortality in certain patients (i.e., patients with elevated serum creatinine levels or patients who develop secondary infections after SOLU-MEDROL).

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.

Usage in pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential 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.

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 or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of SOLU-MEDROL Sterile Powder 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 appropriate antituberculous 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.

Because rare instances of anaphylactic (eg, bronchospasm) 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.

There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large IV doses of SOLU-MEDROL (greater than 0.5 gram administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox 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 not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS

General precautions

Drug-induced secondary adrenocortical insufficiency 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 reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible 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 should 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.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

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

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see **DOSAGE AND ADMINISTRATION**).

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and methylprednisolone; therefore, it is possible that adverse events associated with the individual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of methylprednisolone and may require increases in methylprednisolone dose to achieve the

desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity. Methylprednisolone may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox 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
Severe arthralgia
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones
Osteoporosis
Tendon rupture, particularly of the Achilles tendon

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis
Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Dermatologic

Impaired wound healing
Thin fragile skin
Petechiae and ecchymoses
Facial erythema
Increased sweating
May suppress reactions to skin tests

Neurological

Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment
Convulsions
Vertigo
Headache

Endocrine

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
Menstrual irregularities
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic

Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos

Metabolic

Negative nitrogen balance due to protein catabolism

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

Hyperpigmentation or hypopigmentation
Subcutaneous and cutaneous atrophy
Sterile abscess
Anaphylactic reaction with or without circulatory collapse, cardiac arrest, bronchospasm
Urticaria
Nausea and vomiting
Cardiac arrhythmias; hypotension or hypertension

DOSAGE AND ADMINISTRATION

When high dose therapy is desired, the recommended dose of SOLU-MEDROL Sterile Powder is 30 mg/kg administered intravenously over at least 30 minutes. This dose may be repeated every 4 to 6 hours for 48 hours.

In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized; usually not beyond 48 to 72 hours.

Although adverse effects associated with high dose short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

In other indications initial dosage will vary from 10 to 40 mg of methylprednisolone depending on the clinical problem being treated. The larger doses may be required for short-term management of severe, acute conditions. The initial dose usually should be given intravenously over a period of several minutes. Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and

clinical condition. Corticoid therapy is an adjunct to, and not replacement for conventional therapy.

Dosage may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg per kg every 24 hours.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

SOLU-MEDROL may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution as directed. The desired dose may be administered intravenously over a period of several minutes. If desired, the medication may be administered in diluted solutions by adding Water for Injection or other suitable diluent (see below) to the **Act-O-Vial** and withdrawing the indicated dose.

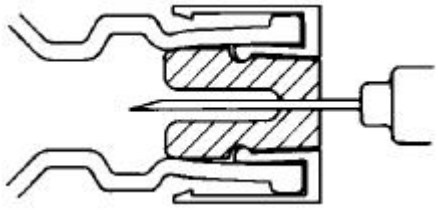
To prepare solutions for intravenous infusion, first prepare the solution for injection as directed. This solution may then be added to indicated amounts of 5% dextrose in water, isotonic saline solution or 5% dextrose in isotonic saline solution.

Multiple Sclerosis

In treatment of acute exacerbations of multiple sclerosis, daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.
5. Insert needle **squarely through center** of stopper until tip is just visible. Invert vial and withdraw dose.



STORAGE CONDITIONS

Protect from light.

Store unreconstituted product at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Store solution at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Use solution within 48 hours after mixing.

HOW SUPPLIED

SOLU-MEDROL Sterile Powder is available in the following packages:

40 mg Act-O-Vial System (Single-Dose Vial)
25 x1 mL NDC 0009-0039-28

125 mg Act-O-Vial System (Single-Dose Vial)
25 x 2 mL NDC 0009-0047-22

500 mg Act-O-Vial System (Single-Dose Vial)
4 mL NDC 0009-0003-02

1 gram Act-O-Vial System (Single-Dose Vial)
8 mL NDC 0009-0018-20

500 mg (Multi-Dose Vial)
8 mL NDC 0009-0758-01

1 gram (Multi-Dose Vial)
16 mL NDC 0009-0698-01

REFERENCES

[1]Fekety R. Infections associated with corticosteroids and immunosuppressive therapy. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. Philadelphia: WBSaunders Company 1992:1050-1.
[2]Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticoids. *Rev Infect Dis* 1989:11(6):954-63.

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