PT PFIZER INDONESIA
LOCAL PRODUCT DOCUMENT

Generic Name: Methylprednisolone Sodium Succinate
Trade Name: SOLU-MEDROL®
CDS Effective Date: January 03, 2018
Supersedes: January 14, 2016

For Intravenous or Intramuscular Administration

SOLU-MEDROL 125 mg: each vial contains methylprednisolone sodium succinate equivalent to methylprednisolone 125 mg

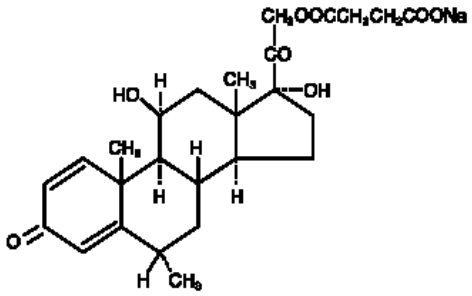
SOLU-MEDROL 500 mg: each vial contains methylprednisolone sodium succinate equivalent to methylprednisolone 500 mg

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.

ACTIONS

Methylprednisolone is a potent anti-inflammatory actions steroid synthesized in the Research Laboratories of Upjohn Company. It has a 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.

PHARMACOLOGICAL PROPERTIES

Preclinical safety data

Based on conventional studies of safety pharmacology and repeated-dose toxicity, no unexpected hazards were identified. The toxicities seen in the repeated-dose studies are those expected to occur with continued exposure to exogenous adrenocortical steroids.

Carcinogenesis:

Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. Variable results have been obtained with other glucocorticoids tested for carcinogenicity in mice and rats. However, published data indicate that several related glucocorticoids including budesonide, prednisolone, and triamcinolone acetonide can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats. These tumorigenic effects occurred at doses which were less than the typical clinical doses on a mg/m^2 basis.

Mutagenesis:

Methylprednisolone has not been formally evaluated for genotoxicity. However, methylprednisolone sulfonate, which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* at 250 to 2,000 µg/plate, or in a mammalian cell gene mutation assay using Chinese hamster ovary cells at 2,000 to 10,000 µg/mL. Methylprednisolone suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes at 5 to 1,000 µg/mL. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is

structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* and *Escherichia coli* strains at 312 to 5,000 µg/plate. In a Chinese hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested 1,500 µg/mL.

Reproductive toxicity:
Corticosteroids have been shown to reduce fertility when administered to rats. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids, such as methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation.

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

- Non-suppurative 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
- Epicondylitis
- Synovitis of osteoarthritis
- Acute non-specific tenosynovitis
- Rheumatoid arthritis, including juvenile
- Acute gouty arthritis rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Psoriatic arthritis
- Ankylosing spondylitis
- Acute and subacute bursitis

3. Collagen Diseases (Immune Complex Disease)

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

- Systemic lupus erythematosus (and lupus nephritis)
- Acute rheumatic carditis
- Systemic dermatomyositis (polymyositis)

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
- Drug hypersensitivity reactions
- Contact dermatitis
- Urticarial transfusion reactions
- Atopic dermatitis
- Acute non-infectious laryngeal edema (epinephrine is the first drug of choice)
- Serum sickness

- Seasonal or perennial allergic rhinitis

6. Ophthalmic Diseases

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

- Herpes zoster ophthalmicus
- Sympathetic ophthalmia
- Iritis, iridocyclitis
- Chorioretinitis
- Allergic conjunctivitis
- Diffuse posterior uveitis and choroiditis
- Allergic corneal marginal ulcers
- Optic neuritis
- 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
- Loeffler's syndrome not manageable by other means
- Berylliosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- Aspiration pneumonitis

9. Hematologic Disorders

- Acquired (autoimmune) hemolytic anemia
- Erythroblastopenia (RBC anemia)
- Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)
- Congenital (erythroid) hypoplastic anemia
- Secondary thrombocytopenia in adults

10. Neoplastic Diseases

For palliative management of:

- Leukemias and lymphomas in adults
- Acute leukemia of childhood
- Terminal Cancer:
- To improve quality of life in patients with terminal cancer.

11. Edematous States

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

12. Nervous System

- Cerebral edema from tumor-primary or metastatic and/or associated with surgical or radiation therapy
- Acute exacerbations of multiple sclerosis
- Acute spinal cord injury. The treatment should begin within 8 hours of injury.

13. Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.
For use by the intrathecal route of administration.
For use by the epidural route of administration.
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.
Premature infants, because vials contain Benzyl Alcohol. Benzyl Alcohol has been reported to be associated with a fatal "Gasping syndrome" in premature infants.

WARNINGS

Immunosuppressant Effects/Increased Susceptibility to Infections

Corticosteroids may increase susceptibility to infection, 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 in 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. 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.

Person who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or even fatal course in children or adults on immunosuppressant corticosteroids. In such children, or adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled

intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

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 non-immunosuppressive dose of corticosteroids.

While on corticosteroid, therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and the lack of antibody response.

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 anti-tuberculosis 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.

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

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses, and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

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).

Ocular Effects
Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible cornea perforation.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

Usage in Pregnancy
Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. Adequate human reproductive studies have not been done with corticosteroids. Therefore, the use of this drug in pregnancy, nursing mothers, or women of childbearing potential requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or fetus. Since there is inadequate evidence of safety in human pregnancy, this drug should be used in pregnancy only if clearly needed.

Corticosteroids readily cross the placenta. One retrospective study found and increased incidence low-birth weights in infants born of mothers receiving corticosteroids. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. There are no known effects of corticosteroids on labor and delivery. Corticosteroids are excreted in breast milk.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

The following statement applies only when benzyl alcohol is included in the formulation:
Benzyl alcohol can cross the placenta (see sections **WARNINGS** and **PRECAUTIONS)**

Immune System Effects
Because rare instances of anaphylactic (e.g., 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.

Cardiac Effects
Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk

factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

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 g 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.

Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Vascular Effects
Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

Steroids should be used with caution in patients with hypertension.

Injury, Poisoning and Procedural Complications
Systemic corticosteroids are not indicated for, and therefore, should not be used to treat traumatic brain injury, a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo (1.18 relative risk). A causal association with methylprednisolone sodium succinate treatment has not been established.

PRECAUTIONS

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

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

Drug-induced secondary adrenocortical insufficiency may therefore, 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.

A steroid "withdrawal syndrome", seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.

Psychiatric Effects
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.

Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Nervous System Effects
Corticosteroids should be used with caution in patients with seizure disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis.

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**).

Severe medical events have been reported in association with the intrathecal/epidural routes of administration (see section **ADVERSE REACTIONS**).

There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

Gastrointestinal Effects
High doses of corticosteroids may produce acute pancreatitis.

Corticosteroid should be used with caution in non-specific 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, or myasthenia gravis.

There is no universal agreement on whether corticosteroids *per se* are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

Hepatobiliary Effects
Drug-induced liver injury, such as acute hepatitis can result from cyclical pulsed IV methylprednisolone (usually at doses of 1 gm/day). The time to onset of acute hepatitis can be several weeks or longer. Resolution of the adverse event has been observed after treatment was discontinued.

Renal and Urinary Disorders
Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone.

Corticosteroids should be used with caution in patients with renal insufficiency.

Investigations
Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are 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.

Use in Children
The following statement applies only when benzyl alcohol is included in the diluent:

Benzyl alcohol is contained in the accompanying diluents. Benzyl alcohol has been reported to be associated with a fetal "Gasping Syndrome" in premature infants.

The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk

of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such regimen should be resisted to the most urgent indications. Alternate-day glucocorticoid therapy usually avoids or minimizes this side effect.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High dose of corticosteroids may be produce pancreatitis in children.

Metabolism and Nutrition
Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse events associated with the individual use of either drug may be more apt to occur.

Musculoskeletal Effects
An acute myopathy has been described with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular booking drugs (e.g., 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.

Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Other
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.

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.

Aspirin and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids.

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

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

Information for the Patient
Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles, if exposed, to obtain medical advice.

FERTILITY, PREGNANCY AND LACTATION

Fertility
Corticosteroids have been shown to impair fertility in animal studies (see section **Preclinical safety data**).

Pregnancy
Since adequate human reproductive studies have not been done with methylprednisolone sodium succinate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Some corticosteroids readily cross the placenta. One retrospective study found an increased incidence of low-birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, although neonatal adrenal insufficiency appears to be rare in infants who were exposed *in utero* to corticosteroids.

There are no known effects of corticosteroids on labor and delivery.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

The following statement applies only when benzyl alcohol is included in the diluent:

Benzyl alcohol can cross the placenta. (See Section **PRECAUTIONS**)

Lactation
Corticosteroids are excreted in breast milk. No specific data is known for methylprednisolone sodium succinate. This medicinal product should be used during breast feeding only after a careful assessment of the benefit risk ratio to the mother and infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

ADVERSE REACTIONS

The following adverse reactions have been reported with the following contraindicated routes of administration: Intrathecal/Epidural: Arachnoiditis, bowel/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizure, sensory disturbance.

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Frequency not known (cannot be estimated from the available data)**
Infections and infestations						Opportunistic infection, Infection, Peritonitis[#]
Blood and lymphatic system disorders						Leukocytosis
Immune system disorders						Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders						Cushingoid, Hypopituitarism, Steroid withdrawal syndrome
Metabolism and nutrition disorders						Metabolic acidosis, Sodium retention, Fluid retention, Alkalosis hypokalaemic, Dyslipidaemia, Glucose tolerance impaired, Increased insulin requirement (or oral hypoglycemic agents in diabetics), Lipomatosis, Increased appetite (which may result in Weight increased)
Psychiatric disorders						Affective disorder (including Depressed mood, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation), Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia), Mental disorder, Personality change, Confusional state, Anxiety, Mood swings, Abnormal behaviour, Insomnia, Irritability
Nervous system disorders						Epidural lipomatosis, Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]), Seizure, Amnesia, Cognitive disorder, Dizziness, Headache
Eye disorders						Chorioretinopathy, Cataract, Glaucoma, Exophthalmos
Ear and labyrinth disorders						Vertigo
Cardiac disorders						Cardiac failure congestive (in susceptible patients),

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Frequency not known (cannot be estimated from the available data)**
						Arrhythmia
Vascular disorders						Thrombosis, Hypertension, Hypotension
Respiratory, thoracic and mediastinal disorders						Pulmonary embolism, Hiccups
Gastrointestinal disorders						Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage), Intestinal perforation, Gastric haemorrhage, Pancreatitis, Oesophagitis ulcerative, Oesophagitis, Abdominal distension, Abdominal pain, Diarrhoea, Dyspepsia, Nausea
Hepatobiliary disorders						Hepatitis†
Skin and subcutaneous tissue disorders						Angioedema, Hirsutism, Petechiae, Ecchymosis, Skin atrophy, Erythema, Hyperhidrosis, Skin striae, Rash, Pruritus, Urticaria, Acne, Skin hypopigmentation
Musculoskeletal and connective tissue disorders						Muscular weakness, Myalgia, Myopathy, Muscle atrophy, Osteoporosis, Osteonecrosis, Pathological fracture, Neuropathic arthropathy, Arthralgia, Growth retardation
Reproductive system and breast disorders						Menstruation irregular
General disorders and administration site conditions						Impaired healing, Oedema peripheral, Fatigue, Malaise, Injection site reaction
Investigations						Intraocular pressure increased, Carbohydrate tolerance decreased, Blood potassium decreased, Urine calcium increased, Alanine aminotransferase increased,

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency not known (cannot be estimated from the available data)
						Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood urea increased, Suppression of reactions to skin tests*
Injury, poisoning and procedural complications						Spinal compression fracture, Tendon rupture

The following adverse reactions have been reported with the following contraindicated routes of administration: Intrathecal/Epidural: Arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizure, sensory disturbance. The frequency of these adverse reactions is not known.

* Not a MedDRA PT

† Hepatitis has been reported with IV administration (see section 4.4 Special warnings and precautions for use).

Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4 Special warnings and precautions for use).

OVERDOSAGE

There is no clinical syndrome of acute overdosage with corticosteroids. Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. Methylprednisolone is dialyzable.

INTERACTIONS

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS – Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity.

CYP3A4 INDUCERS – Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrate

for CYP3A4. Co-administration may require an increase in methylprednisolone dosage to achieve the desires result.

CYP3A4 SUBSTRATES – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with co-administration.

NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are with methylprednisolone are described in table below.

Table below provides a list and descriptions of the most common and/or clinically important drug interactions or effects with methylprednisolone.

Important drug or substrate interactions/effects with methylprednisolone

Drug Class or Type DRUG or SUBSTANCE	**Interaction/Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS

Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see sections WARNINGS and PRECAUTIONS). 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITORS (and SUBSTRATES)
Contraceptives (oral) - ETHINYLESTRADIOL/NORETHINDRONE	CYP3A4 INHIBITORS (and SUBSTRATES)

- GRAPEFRUIT JUICE	CYP3A4 INHIBITORS
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon co-administration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITORS
NSAIDs (non-steroidal anti-inflammatory drugs) - High-dose ASPIRIN (Acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium depleting agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta-2-agonists.

Incompatibilities

To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate be administered separately from other compounds

that are administered via the IV route of administration. Drugs that are physically incompatible in solution with methylprednisolone sodium succinate include but are not limited to: allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol.

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 maybe 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/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.

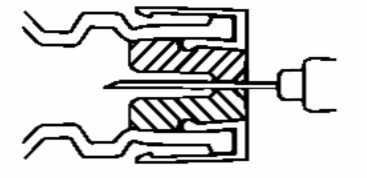
NOTE: Some of the Methylprednisolone sodium succinate formulations come with a diluent that contains benzyl alcohol (see section **PRECAUTIONS**, Use in Children). The amount of benzyl alcohol per each vial is 18 mg.

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.

Note: Steps 1-4 must be completed before proceeding.

5. Insert needle squarely through center of stopper until tip is just visible.
6. Invert vial and withdraw dose.



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

STORAGE CONDITIONS

Store unreconstituted product at controlled room temperature maximum 30°C.
Store solution at controlled room temperature maximum 30°C.
Use solution within 48 hours after mixing.

HOW SUPPLIED

SOLU-MEDROL 125 mg Act-O-Vial System (with sterile solvent), Reg. No. DKI9586100744B1
SOLU-MEDROL 500 mg Vial System (with sterile solvent), Reg.No. DKI9586100744C1

HARUS DENGAN RESEP DOKTER

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